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Editorial

Anaphylaxis

New Products

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Review

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Anaphylaxis

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The review article of this issue is a critical appraisal of the anaphylaxis guidelines. Pfizer's vaccine against COVID-19 began to be given to healthcare professionals in Japan, and it was found that it caused anaphylaxis as frequently as 1 in 4,400 persons (see page 21).

A TV drama "Unsung Cinderella," in which a hospital pharmacist is the main character showed an anaphylactic shock case caused by a wasp in the first episode. The ER doctor of the hospital where the patient was transported ordered the pharmacist to prepare an intramuscular injection of 0.3 mg of adrenaline.

The doctor also directed the preparation of corticosteroids and antihistamines. Despite using adrenaline three times, the patient developed cardiac arrest. It is a condition considered to be refractory anaphylactic shock. When the doctor was wondering why adrenaline didn't work, the pharmacist found a medicine bag labeled bisoprolol in the pocket of the patient's pants and said, "The patient may be using a beta blocker. I urge glucagon administration." The doctor injected glucagon intravenously, suspiciously. The patient then recovered. The medical supervision of the official blog of this drama explains that glucagon exerts a cardiotonic effect other than β receptors.

The use of glucagon in this context is gaining worldwide recognition, but in reality it is groundless. As is clear from our review, bisoprolol is a β_1-selective β-blocker and does not affect the β_2 action of adrenaline, which is the essential pharmacological base for the treatment of anaphylaxis. Therefore, it turns out that glucagon is overrated not only in this drama but also in the most anaphylaxis guidelines.

Another important issue with anaphylaxis guidelines is that the position of corticosteroids essential for anaphylaxis is lower than that of antihistamines. It is strange that the evaluation of corticosteroids is low not only in Japan but also all over the world. Anaphylaxis develops suddenly, and most doctors who treated it did use corticosteroids, making comparative studies impossible now. Therefore, there is no choice but to properly analyze observational studies, but the situation is critical that an essential treatment with corticosteroids for anaphylaxis can be burried with incorrect analysis.

If you read the review article "Critical appraisal of anaphylaxis guidelines" carefully, you will be able to treat patients without hesitation when you experience anaphylaxis.

Vaccines for COVID-19: Is it useful in Japan?

For both elderly and young people, harm outweighs benefit. For medical/welfare workers, unknown due to lack of data.

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Med Check Editorial Team

Abstract

● RNA vaccines manufactured by Pfizer Biontech (BNT) and Moderna (MOD) are being inoculated around the world as vaccines provisionally approved for COVID-19 (emergency use authorization).

● From the published information, the suppression rate of COVID-19 with onset (overt infection = symptomatic and PCR positive cases) is 82 to 90% at about 2 to 3 months after the first dose, and about 95% for 1.5 to 2 months 1 to 2 weeks after the second dose. There was no difference among age groups. They prevented severe COVID-19 by 90% or higher, but the preventive effect on death is unknown.

● The suppression rate of COVID-19 with onset by AstraZeneca's vaccine (AZD) which is a viral vector vaccine is 60%. It is inferior to that of the other two vaccines (mRNA vaccine), and autoimmune neurological diseases were observed at a high rate: 10 to 80 times higher than that in the general population. Incidence of and mortality from deep vein thrombosis especially cerebral venous sinus thrombosis is extremely high.

● The preventive effect on asymptomatic infection of COVID-19 (PCR positive without onset) is unknown with BNT and MOD, but AZD was totally ineffective.

● Incidence of serious adverse events is not different from that in placebo in both mRNA vaccines, but severe adverse events, such as fever and pain, are observed 1.7 to 2.5 times more frequently than in placebo in a short-term after vaccination.

● In Norway, 1 in 1300 elderly people who received the vaccine has died, and causal relation with the vaccine has been suspected. In the case of Hank Aaron's death (sudden death during sleep 2 weeks after vaccination), the causal relationship with the vaccine cannot be denied. The long-term harm of vaccines, such as other autoimmune diseases and nervous system disorders, is totally unknown.

● We calculated how many people should be vaccinated in order to reduce 1 death from COVID-19 in Japan, assuming that the vaccine has the maximum suppression rate of COVID-19 with onset and the number of death due to COVID-19 is fairly high in Japan. We found that 1700, 6400, 20,000, 60,000, 200,000, 600,000 and 2 million people need to be vaccinated to prevent 1 death from COVID-19 in people aged 80 and over and those in their 70s, 60s, 50s, 40s, 30s and 20s, respectively.

● In other words, even if the effect of vaccine is assumed to be maximum and the harm is minimum, in those aged 80 and over, whose incidence of severe COVID-19 and mortality are high, the number of death from the vaccine is estimated to be higher than the number of deaths it can reduce.

● For medical and welfare workers who have a higher chance of infection, the benefits may outweigh the harms, but since there is no data on mortality among this high-risk group, accurate analysis cannot be made.

Conclusion: Harm may outweigh benefits for both older and younger people
Harm-benefit balance is unknown for medical and welfare workers due to a lack of data.

Keywords:
vaccine, onset suppression rate, asymptomatic infection suppression rate, death of the elderly, sudden death during sleep, anaphylaxis

Introduction

We made preliminary analysis for COVID-19 vaccines (candidates) before authorization in Med-Check in English No. 19 [1] and related materials [2].

As of February 10th, 2021, RNA vaccines developed by Pfizer and Biontech (BNT162b2, hereinafter "BNT"), and Moderna (mRNA1273, hereinafter "MOD"), and a viral vector vaccine developed by AstraZeneca (AZD1222, hereinafter "AZD") have received emergency use authorization and are now the main vaccines used against COVID-19 [3-5]. Since their approval is just provisional, they are "vaccine candidates", but to make it simple, they are referred to as "vaccines" in this article.

Summaries of phase 3 trials (BNT [6], MOD [7]) and trials up to Phase 3 (AZD) [8] have been published for each vaccine as well as results of regulatory evaluation [9-11].

It has been reported that in Israel, 80% of the population aged 70-79 has completed the second vaccination at the end of January [12]. In Norway, 1 in 1300 people aged 75 and over who received vaccination has died, and the relationship with the vaccine has been suspected [13].

The points for evaluating harm and efficacy of the vaccines

The important points we considered when we examined the efficacy and safety of these vaccines were whether the reported 95% protection against COVID-19 is true or not, safety and the balance between them. We also reviewed how many people must be vaccinated to reduce aggravation, especially death, due to COVID-19 in case inoculation is widely implemented in Japan. The analysis was made by age based on the cumulative number of deaths as of February 3rd, 2021 [14].

The difference in the mechanism of action between mRNA vaccine and viral vector vaccine are basically as

Table 1: Comparison of 3 major vaccines

			Manufacturers	Pfizer/BionTec (BNT)	Moderna (MOD)	AstraZeneca (AZD)
Basic information			Status of approval	Emergency Use Authorization (EUA)		
			Type of vaccine	mRNA	mRNA	Virrus Vector
			Control group	Normal saline (NS)	Normal saline (NS)	meningococcal vaccine
			masking/blinding	participants, investigator	participants, observer	participants only
			Primary outcome	COVID-19 with onset (symptomatic & positive PCR testing)		
			Age of participants	16～(>=65: 21%)	18～(>=65: 25%)	18～(>=56: 12%)
			No of participants	about 40,000	about 30,000	about 12,000
			1 week after 2nd dose Participants (Person-year)	18,000(2200PY)/group	13,000(？PY)/group	5,800(1,300PY)/group
Efficacy: protection rate (%)			Onset after the 1st dose	82% (50 vs 275)	90% (35 vs 332)	frequent amendment of protocol, contradictory data
			Onset after the 2nd dose	95.0% (8 vs 162)	94.1 (12 vs 204)	59.5% (standard dose) *e
			Severe COVID-19	96% (1 vs 39) NNTB＝300/year *a		0 vs 2
			asymptomatic COVID-19 (positive PCR only)	Unknown	Unknown	No effect (0%) *f
Harm Adverse Events (AE)	Local		Pain	66～83%	89%(4%)	80%近く
	Systemic		Fever (severe)	11～16%(1%)	15%(1%)	headace was reported 60% without paracetamol and more than 40 % with 4 g/day of paracetamol.
			Headach (severe)	39～59%(3～5%)	59%(5%)	
			muscle pain (severe)	29～37%(1～2%)	66%(10%)	
			Althralgia (severe)	19～22%(1～2%)	43%(5%)	
			Any AE (Severe)		79%(16%)	
			Adverse Events (AE) % Odds Ratio (OR)、p value	Severe AE: 1.1% vs 0.6% OR=1.7,p<0.00001	related severeAE: 0.5% vs 0.2% OR=2.5, p<0.00001 *b	2 Case with transverse myelitis or multiple sclerosis were reported among 1280 person-year (PY) of observation: 156/100,000 PY *g
			Death	2 vs 4	2 vs 3(4) *c	1 vs 4 *d

* a: This means that 200 persons need to be vaccinated to reduce the number of severe COVID-19 disease among population in which 1 of 190 persons develop severe COVID-19 annually.
* b: Fever with 40℃ or higher (life-threatening or grade 4) in 13 patients and life-threatening vomiting in 1 patient in MOD group and only 3 patients had fever with 40℃ or higher in Placebo group.
* c, d: One of them died from COVID-19, and all others died unrelated to COVID-19.
* e: According to EU product information [11].
* f: There was no protection effect of asymptomatic or symptoms unknown COVID-19. Including these, the protection rate of PCR test positive persons was 46.3%.
* g: 156 / 100,000 person-years is equivalent to 13 to 80 times the incidence of multiple sclerosis in general population (2 to 12 per 100,000 person-years).

follows. The former is directly taken up by macrophages and produces spike proteins of antigenic substances in macrophages. On the other hand, the latter works in 2 steps. It first infects cells other than macrophages and produces spike proteins in them which are recognized by antigen producing cells or macrophages and then destroyed by cell-mediated immunity. (See [15-23]).

Clinical efficacy

Table 1 summarizes the characteristics (basic properties, efficacy and harm) of the 3 preparations. We will explain about each of them below following the data on the table.

Pfizer/Biontech's preparation (BNT)

A phase 3 study for BNT [6,9] is a randomized placebo-controlled trial (RCT), in which a half of the participants (age 16 and above) were injected with BNT and the other half with saline as placebo. Approximately 20,000 participants received one or more injections in each group, and they were observed for more than 1 week after the second shot. At baseline, in each group, 18,000 participants had no COVID-19. The observation was carried out for 46 days, about 2300 person-years in each group.

No difference was found in baseline characteristics between the 2 groups. However, at the time of 2-month follow-up (mean duration), 37,306 people were included, while 43,448 people had received one or more shots after randomization. This means that 5742 people had been withdrawn in the process. The biggest question is why they dropped out, but it is unknown because the reasons of withdrawal were not reported.

Confirmed COVID-19 with onset was defined as the presence of at least one of the following symptoms: fever, new or increased cough, new or increased shortness of breath, chills, new or increased muscle pain, new loss of taste or smell, sore throat, diarrhea, or vomiting, combined with a respiratory specimen obtained during the symptomatic period or within 4 days before or after it that was positive for SARS-CoV-2 by PCR testing.

As shown in the formula below, protection rate (%) against COVID-19 with onset is the ratio of the difference between the incidence in placebo group and vaccine group to the incidence in the placebo group, and this is considered as the efficacy rate of the vaccine.

$$\frac{\text{(incidence in placebo group} - \text{incidence in vaccine group)}}{\text{incidence in placebo group}}$$

Efficacy (protection rate) after the first dose is 82% (50 in BNT vs 275 in placebo). The primary outcome, efficacy rate 7 days after the second dose (excluding patients who were already infected at the time of vaccination), is 95% (8 in BNT vs 162 in placebo). There is no major difference by age (93.7%-95.6%).

Prevention rate for aggravation is 89% (1 in BNT vs 9 in placebo). When MOD is included, it is 96%. In other words, the vaccine prevented aggravation in 1 in 300 persons annually in the high-risk group in which 1 in 200 persons experience aggravation annually. Two persons and 4 persons died in BNT and placebo groups, respectively, during the study, and no COVID-19 related death has been reported. Severity of the symptoms was judged by medical experts from Pfizer, who were not informed of the treatment assignment ([6] protocol).

There are no comparative data on asymptomatic infection, and preventive effect for such cases is unknown.

Serious adverse events have been reported at similar frequency in both groups. However, although details are unknown, some kind of adverse events (adverse reactions) associated with the vaccine occurred in 21% of the participants in BNT and 5 % of the participants in placebo (odds ratio=approximately 5, p <0.00001), and severe adverse events occurred 1.7 times more frequently in the vaccine group. The number of people who needed analgesics or antipyretics due to pain or fever was particularly high after the second dose in BNT group than in placebo group: 45 % vs 13 % in younger subgroup (18 to 55 years) and 38 % vs 10 % in older subgroup (>55 years). Odds ratio were both about 5.6 (p<0.00001).

Moderna's preparation (MOD)

A phase 3 study conducted by Moderna [7,10] is a randomized placebo-controlled trial (RCT), in which about a half of the participants aged 18 years and older were injected with MOD and the other half with saline. About 30,000 people (15,000 people in each group) received one or more injections. At the start of the study, 27,000 participants in both groups had no COVID-19 and were followed at least 2 weeks after the second dose (duration

of follow up: 3400 person-years in each group).

In this study, the participants and observers were masked, but investigators were not, meaning that the trial was not properly double-masked. This means that inoculators knew the assignment, and there might have be subtle difference in how they dealt with participants in the two groups.

The protection rates was 90% after the first dose and 94% at least 14 days after the second dose, which was almost the same result as that with BNT. There is no comparative data on asymptomatic infections, and protection of overall infection is unknown also on MOD.

Regarding harm, some kind of serious reactions occurred in 20% of the participants in MOD group. In addition, related adverse events (adverse reactions) were found 2.5 times more frequently in the vaccine group: 71 (0.5%) with MOD vs. 28 (0.2%) with placebo. It is also noteworthy that fever above 40℃ (rated as grade 4 = life-threatening) or life-threatening vomiting occurred in 1 in 1000 people in the MOD group. These are critical because they may cause death in the elderly.

Note 1:In our article in Med-Check in English No 19 [1], it was estimated to be about 1600 person-years, but the published data revealed that it was 1280 person-years [8].

AstraZeneca's preparation (AZD)

The reports on AZD [8,11] are mainly Phase 2/3 and Phase 3 trials, but they also include two Phase 1/2 trials. In both Phase 2/3 and Phase 3 trials, only the participants were masked, but inoculators and observers were not. Even so, follow-up was carried out for maximum 1300 person-years, and only 680 person-years from 2 weeks after the second inoculation. Efficacy rate is 60% which is lower than BNT and MOD. This result is consistent with that of the animal experiment with monkeys.

Total 34 and 37 patients with subclinical infection (asymptomatic or unknown symptom) were reported in AZD and control groups, respectively, and prevention rate was 7.8% (no significant difference). However, when the numbers of people with symptoms (63 vs 150) were subtracted from the numbers of participants with PCR positive (102 vs 189), and were compared, the prevention rate turned out to be 0%.

Intramuscular injection of AZD does not induce IgA antibody that protects against infection in the nose and pharynx. In animal studies, viral load in the nasopharynx was not different from that of the control group, and no protective effect against COVID-19 infection was observed. The fact that subclinical infection is not prevented in humans is in accordance with the theory, and is quite predictable from the results of animal experiments.

On the other hand, in the observation for 1280 person-years (Note 1), total 2 cases of autoimmune neurological diseases were reported: 1 case with transverse myelitis and 1 apparent case with multiple sclerosis. This is 156 per 100,000 person-years (95% confidence interval: 18.9-563). It is a very high rate: 10-80 times higher than that of incidence rate of multiple sclerosis in general population (2 to 12 per 100,000 persons-years).

In Norway, 1 in 1300 elderly people died

In Norway, 42,000 elderly people aged 75 and over were vaccinated with BNT, and 33 died within a few days after the vaccination [24]. Norwegian Medicines Agency has investigated 13 of the deaths so far and concluded that common adverse reactions of mRNA vaccines, such as fever, nausea, and diarrhoea, may have contributed to fatal outcomes in some of the frail patients. The Norwegian Institute of Public Health said that for those with the severest frailty even relatively mild side effects can have serious consequences and that the benefits of the vaccine to those with a very short life expectancy may be marginal or irrelevant. It also recommended that doctors carefully consider the benefits and disadvantages of giving the vaccine to extremely frail patients (such as those whose frailty is ranked 8 or 9 on the Clinical Frailty Scale or equivalent) and terminally ill patients ahead of vaccination. [24].

For example, as described above, a clinical trial has reported that MOD caused life-threatening fever above 40 ℃ or life-threatening vomiting in 1/1000 people [7]. If this happens in the frail elderly, it can actually lead to death.

Hank Aaron's death may also be related

Hank Aaron, an 86-year-old former major league legend and home run king who overtook Babe Ruth, received the first dose of Moderna's vaccine for COVID-19 with his wife on January 5, 2021, and the news was covered by the media [25]. It was supposed to

be a message to black Americans that "vaccines are safe". He wrote in Twitter "I was proud to get the COVID-19 vaccine earlier today at Morehouse School of Medicine. I hope you do the same! " [26] . However, on January 22nd, 17 days after the injection, he died during sleep. It was reported that no other cause of death had been identified [25].

After his death was reported, the relationship with the vaccine was denied by a flood of comments insisting that the death followed a natural course [27,28].

The relationship between sudden infant death syndrome (SIDS) or unexpected sudden death (SUD) and vaccination is epidemiologically confirmed [29-31] (Note 2). A series of sudden deaths due to Hib and pneumococcal vaccines led to the suspension of vaccination in March, 2011. Although it was resumed after one month, the relationship between vaccination and sudden death was highly suspected [30,31].

After that, 50 cases diagnosed with SIDS by forensic autopsy were examined in Japan. Vaccination was confirmed in 32 cases. Among them, it was reported that vaccine was given 7 days before death in 7 cases, and the association with the vaccine is strongly suspected [32]. Many cases have been reported, in which twins died suddenly on the same day after vaccination [33-35], suggesting a very strong relationship between vaccination and sudden death.

Note 2: Meta-analysis result of case-control studies [36] indicates that vaccination was effective in halving the incidence of SIDS. However, these studies ignore "healthy vaccinee effect", meaning that vaccinated people are usually healthy and those with fever or illness would avoid vaccination [29-31]. It can be considered that these studies showed the opposite result because of this effect.

Why sudden death occurs after vaccination

This question was discussed in Med-Check No. 43 [31] and TIP 2011 April Issue [30]. When hypoxemia occurs for some reason, the respiratory center of the brain normally senses a lack of oxygen and orders to promote breathing by respiratory drive function and increase oxygen concentration. However, it is believed that if this mechanism is impaired by drugs (Tamiflu, sleeping pills, opioids, etc.), bacterial toxins, and inflammatory conditions due to infectious diseases, respiratory drive does not function in hypoxic condition, leading to deterioration and respiratory arrest.

Apnea due to inflammation not only in infants but also in adults

Let us explain the mechanism of inflammation-related loss of respiratory drive. Inflammations occur not only by infections, allergy and vaccines, but also non-infectious non-allergic inflammations occur. The latter are the process of repairing injuries caused by severe obesity and/or by ischemia-reperfusion injuries (caused by sustained stress and its withdrawal). Interleukin-1β(IL-1β), a type of pro-inflammatory cytokine, enhances cycloxygenase which produces prostaglandin E2, an inflammatory substance, in the cells of the capillaries of the brain, and releases it into the brain. It acts on the respiratory center in the medulla oblongata, impairing the respiratory drive and suppressing breathing. It is believed that hypoxia induces tissue injuries with inflammation which increase of prostaglandin E2 production more, causing a vicious cycle of hypoxia and respiratory arrest [37,38].

These are the findings from animal studies that correspond to human infants [37,38], but similar effects have been observed even after some growth[37, 39].

This mechanism also applies to "sleep apnea syndrome" in adults. The syndrome is believed to be primarily caused by obesity-induced airway obstruction [40], but this is not the only cause.

In highly obese people, cytokines, such as TNF-α and interleukin (IL, especially IL-6 and IL-1β), are induced, causing various inflammatory reactions in the body to cause heart disease and diabetes [41]. Moreover, cytokines increase prostaglandin E2, which may cause apnea and hypoxia during sleep. In sleep apnea syndrome, cytokines, such as TNF- α and interleukin, are increased [42]. The condition of high cytokine level due to obesity can cause apnea, and hypoxia caused by apnea can also enhance the condition of high cytokine level, causing increased prostaglandin E2 and inflammation [42], resulting in a vicious cycle [37,38].

Fever and local swelling can be caused by COVID-19 vaccine

With pneumococcal vaccine, nearly 40% of children experience fever, and some percentage to 10% of them develop a temperature of 39℃ and above. One-fifth to one-third of them fall asleep after each vaccination [31].

Vaccines for COVID-19, BNT and MOD, cause fever in about 10% to 20%. They also cause local swelling in response to foreign substances, and substantial amount of inflammatory cytokines are released, leading to inflammatory state, including arthritis etc. It has been reported that mild viral or bacterial infections are also found in 70-80% of SIDS cases [31]. As vaccines create such a condition of infection, it is reasonable to think that they are related.

In the case of Hank Aaron, it can be suspected that mild inflammation was caused by the vaccine, and respiratory drive did not function even at hypoxic condition, leading to progressed hypoxia and sudden death due to respiratory arrest. Regulators and the media deny the causal relationship, insisting that his death followed the "natural course". However, nobody expected that a man who enthusiastically advocated for the vaccine on TV would have respiratory arrest and die from old age 2 weeks after the injection. It is too unrealistic to make it "unrelated".

Anaphylaxis occurs 1 in 4000

In the U.S. and the U.K., it has been reported that anaphylaxis occurred in 5 and 20 persons in 1 million doses, respectively. However, it is based on spontaneous reports and highly inaccurate.

According to a detailed survey at medical institutions in the U.S., anaphylaxis occurred in 270 persons (BNT) or 230 persons (MOD) in 1 million doses [43]. In other words, anaphylaxis occurred in 1 in about 4000 persons.

In Japan, information on anaphylaxis cases has been actively collected and disclosed. The review by the Med-Check Team revealed that anaphylaxis occurred in 132 persons (73%) per 580,000 doses. This means that anaphylaxis occurs in 230 persons in 1 million doses, and approximately 1 in 4400 persons. [44]

Anaphylaxis occurs immediately after vaccination and can be treated by prompt and appropriate medication (adrenaline and corticosteroids). No death has been reported so far. However, since it can be also fatal with delayed or wrong treatment, it requires very careful treatment.

Doctor dies of autoimmune disease

A 56-year-old obstetrician-gynecologist in Miami, the U.S. received the first Pfizer Biontech vaccine on December 18th, 2020. He developed idiopathic thrombocytopenic purpura (ITP) after 3 days and died of cerebral hemorrhage 16 days after vaccination [45].

A characteristic of autoimmune diseases after vaccination, including nervous system disorders such as multiple sclerosis, is that they may occur long after vaccination. Since no long-term observation has been conducted so far, the true nature of harm of COVID-19 vaccines is completely unknown.

Japan's Ministry of Health, Labor and Welfare (MHLW) disclosed that 6 health care workers died within 20 days after one million doses of BNT were inoculated. Of these, all four women died from hemorrhagic stroke, 2 subarachnoidal hemorrhage and 2 intracerebral hemorrhage. The age of one woman was 26 years old. Combined odds ratio of hemorrhagic stroke of women who received vaccination by age, compared with that of general population in 2019 was 9.58 (95%CI: 1.50, 61.17, p=0.017, I2 = 40.9%) while combined all cause mortality by age compared with that of general population in 2019 was 0.08 (95%CI: 0.03, 0.21, p<0.0001, I2 = 5.2%). Reporting odds ratio for mortality from hemorrhagic stroke was 209.7 (95%CI: 9.2, 4590, p<0.0001). Women who received vaccination are far healthier than general population in 2019 but died far more frequently from hemorrhagic stroke.

What would happen when applied in Japan

In Japan, vaccination will start for medical professionals by the end of February. In the published trials of BNT and MOD, the effect of vaccine candidates was tested on a group of people, 7-8% of which was estimated to have symptomatic COVID-19 annually. However, in Japan, morbidity of COVID-19, including asymptomatic infection, is only 0.3% annually. If only with symptomatic infection, the number would be far smaller. As compared to the participants of the trials, morbidity is 1/30-40, and mortality is about 1/30 in Japan.

It should be examined how the vaccines would reduce severe cases as well. However, unfortunately, the cumulative number of severely ill patients has not been published, and the cumulative number by age is also unknown. Only the number of deaths can be analyzed by age. In June 2020, MHLW issued a notification to prefectural governments to report all deaths if SARS-

CoV-2 was positive in the PCR test [46]. Strictly speaking, even deaths from other causes are also counted as deaths from COVID-19. Therefore, the actual number of deaths from COVID-19 should be less than the disclosed data, but for the time being, the data disclosed by the MHLW are used in this article.

On the other hand, because of the scale of the trials and the duration of observation, there was only 1 death from COVID-19 each in control groups in MOD and AZD trials, making it impossible to directly examine the effect on reducing deaths.

Therefore, assuming that the efficacy rate of BNT and MOD (95%) can be applied to the preventive effect on death, and that the preventive effect lasts for 1 year, we examined how useful the vaccines would be in Japan. It is a calculation of how many people in Japan need to be inoculated to reduce 1 death from COVID-19.

The cumulative number of deaths and the number of confirmed infections by age in Japan as of February 3rd, 2021 [14] was published (**Table 2**). Partly because it was very cold this winter compared to last winter, the epidemic is much greater than in the previous two seasons (April and July-August). As of February 14th, death toll is still increasing. Therefore, the number of deaths from the fall of 2020 to the third term may be more than double the number of deaths from the beginning of the third term to date.

We calculated how many people need to be vaccinated in order to reduce 1 death from COVID-19, assuming that the number of deaths in one year until the end of the third term will be double the number of deaths by February 3, this year (**Table 2**). This is to ensure that the effect of the vaccine is not underestimated. We also assumed that the vaccine reduces the number of death by 95%. To avoid misunderstanding, we would like to emphasize here again that the number of deaths that we used for the calculation is fairly high.

The numbers of vaccinees required to reduce 1 death from COVID-19 are 1700, 6400, 20,000, 60,000, 600,000 and 2,000,000 for people aged 80 and over,

Table 2: How many people need to be vaccinated to reduce 1 death from COVID-19 in Japan ?

Age	A. No. of death	B. cumulative no. of COVID-19 patients	C. Population Oct. 2019	D. Suppose the no. of death is double the previous number A×2	E. Expected No. of deaths reduced annually D×0.95	F. NNTB (Japan) How many people need to be vaccinated to reduce 1 death from COVID-19 per year		G. NNTB (UK or US) where 1/600-700 of the population has died		Appendix H. Death from pneumonia (2019)		Appendix I. COVID-19 mortality rate / 100,000
						C/E	Approximate number	population/ (No. death × 2 × 0.95)	Approximate number	No. of death	mortality rate / 100,000	
>= 80	3,437	26,504	11,218,370	6,874	6,530	1,718	**1,700**	59	60	80,001	713.1	30.6
70 -79	1,302	27,240	15,856,385	2,604	2,474	6,410	**6,400**	221	200	14,160	89.3	8.2
60 -69	435	31,373	16,104,287	870	827	19,485	**20,000**	672	700	3,577	22.2	2.7
50 -59	142	49,072	16,035,517	284	270	59,435	**60,000**	2,049	2,000	821	5.1	0.9
40 -49	48	53,354	18,180,527	96	91	199,348	**200,000**	6,874	7,000	288	1.6	0.3
30 -39	12	56,551	13,803,641	24	23	605,423	**60,000**	20,877	20,000	84	0.6	0.1
20 -29	3	83,905	11,822,382	6	6	2,074,102	**2 million**	71,521	70,000	29	0.2	0.0
10 - 19	0	24,070	11,000,299	0	0	infinity		uncalculable		27	0.2	0.0
< 10	0	9,707	9,709,322	0	0	infinity		uncalculable		93	1.0	0.0
unknown	101	8,613										
Total	5,480	370,389	123,730,730	10,960	10,412	11,883	12000	410	400	99,080	80.1	4.4
0-29 total	3	117,682	32,532,003	6	6	5,707,369	**6 millon**	196,806	20万人	149	0.46	0.0

A , B: From outbreak trends of COVID-19 in Japan (preliminary figures) (as of 2001 / 2/3. 18:00) [14]
Approximate number in F: For example, it shows that when 1700 people aged 80 and over are vaccinated, 1 death can be reduced. In people aged below 30, about 6 million people need to be vaccinated to reduce 1 death in Japan.

G: In the U.K. and the U.S., where clinical trials for BNT, MOD, and AZD were conducted, 1 in 600 to 700 people die annually from COVID-19. Since the number of deaths by age in these countries is not available, our calculation is based on the assumption that it was the same as the distribution of deaths by age in Japan. In people aged 80 and over, inoculating 60 people can reduce 1 death per year in UK or in US. This suggests that except for the very frail elderly, the vaccine is worth inoculating.

H: The number of deaths from pneumonia and the annual mortality rate (per 100,000) in 2019.

I: The mortality rate for 1 year since the start of COVID-19 epidemic. In those aged below 70, it is as low as 1/6 to 1/11 of the mortality rate for pneumonia in 2019. For those aged 80 and over, it is even lower: 1/23 of the mortality rate for pneumonia in 2019.
In addition, the number of deaths from pneumonia from February to September 2019 was 60,593, and the number of deaths from pneumonia during the same period in 2020 was 49,467, a decrease of 11,126 (18%). As of the end of September, the number of deaths from COVID-19 is 1564, which is only 1/30 of the number of deaths from pneumonia and 1/7 of the decreased number in deaths from pneumonia.

and those in their 70s, 60s, 50s, 40s, 30s, and 20s, respectively. Since there has been no death in those aged below 20, the vaccine cannot reduce death in this age group at all.

The number of deaths shortly after the vaccination in people aged 75 and over in Norway is higher than the number of deaths the vaccine could save in those aged 80 and over.

Including sudden death during sleep, such as the case of Hank Aaron, whose association authorities have denied, and autoimmune diseases, such as the case of the obstetrician-gynecologist in the U.S., are taken into account, the harm can be greater, not only in the elderly, but also in the younger age groups.

In particular, in people aged below 30, 6 million people are required to be vaccinated in order to reduce 1 death. It is immeasurable how many people will experience anaphylaxis, autoimmune diseases, hemorrhagic strokes and sudden death during sleep if so many doses are given just to reduce 1 death.

Effect for healthcare professionals

In medical and welfare workers, who have a higher chance of infection, the benefit may outweigh the harm. Since there is no data on the mortality rate of these high-risk individuals, it is not possible to make an accurate assessment. However, almost 10 times more frequent sudden deaths from hemorrhagic stroke were already reported in female health care workers who were vaccinated, including one very young woman in her twenties, the age group in which no women have died from COVID-19 in Japan. Decision must be made according to the situation of each individual. We will continue to collect information, and publish them as soon as the data necessary for analysis are available.

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Review

2021 Annual Theme: Critical Appraisal of Treatment Guideline Series (19)

Anaphylaxis: Both adrenaline and corticosteroids are essential

Translated and revised from Med Check (in Japanese) May 2021 ; 21 (95):52-57

Med Check Editorial Team

Abstract

- Anaphylaxis is a life-threatening adverse reaction to medicines, but it can be treated successfully with appropriate treatment.
- The key sign leading to death is that of airway obstruction due to laryngeal edema. It may appear without skin symptoms leading to asphyxia.
- If a patient is diagnosed with anaphylaxis, she/he should be promptly injected with adrenaline intramuscularly and corticosteroids subsequently. Delayed use of adrenaline may threaten patient's life. In particular, its use after cardiac arrest is almost ineffective.
- Adrenaline works via its β_2 action which suppresses mast cell degranulation that is the fundamental cause of anaphylaxis.
- However, resistance against adrenaline is developed and it becomes less effective within one to a few hours. Corticosteroids in turn become effective at that time, so corticosteroids should always be used just after adrenaline. The more severe the anaphylaxis is, the more necessary it is.
- It is appropriate that the guidelines emphasize the importance of adrenaline. However, it is inappropriate to emphasize the pressor and bronchodilator effects of adrenaline rather than the stabilization of mast cells via β_2 receptors.
- The evaluation of corticosteroids is too low in the WAO guidelines. No use of corticosteroids is related to the increased risk of biphasic anaphylaxis by 12-fold.
- If adrenaline and corticosteroids were used appropriately, they work effectively in cases of anaphylaxis exposed with β blockers. There is no evidence base to use glucagon.
- The percentage of people who have experienced anaphylaxis is increasing rapidly. Anybody has a chance to experience anaphylaxis and should be familiar with the initial symptoms of anaphylaxis in order to receive appropriate treatment quickly.

Conclusion: Anaphylaxis should be immediately treated both with adrenaline and corticosteroids.

Keywords:

laryngeal edema, airway obstruction, mast cells, degranulation, β_2 receptors, tolerance, glucagon

Introduction

Vaccination against COVID-19 (so-called novel coronavirus disease) has been in progress also in Japan using Pfizer-BioNTech vaccine since February 17 2021. The incidence of anaphylaxis caused by this vaccine was 230 per million doses [1] (page 21) by our analysis based on the data targeting healthcare professionals

issued by the Japanese Ministry of Health, Labor and Welfare [2]. According to a detailed survey targeting healthcare professionals in the United States., incidence of anaphylaxis induced by Pfizer-BioNTech vaccine was 270 per million doses [3] which is similar to that in Japan.

The number of people who have history of anaphylaxis has been rapidly increasing: the percentage of children/ elementary to high school students who have experienced anaphylaxis was 0.14% (about 1 in 700) in 2004, but increased to 0.48% (about 1 in 200) in 2013 [4]. Food allergies (2.6% to 4.5%) and allergic rhinitis (9.2 to 12.8%) are also increasing, but the degree of increase in anaphylaxis is far more remarkable. It has been reported that 1.6% of people, including adults, have experienced it in the United States [5].

Even if the incidence of anaphylaxis to individual drugs or foods is very rare (i.e. 1 in tens of thousands), there are thousands of drugs and foods, so the total incidence may be considerable.

Anaphylaxis is a serious adverse reaction to drugs that can occur on a daily basis. It is caused by various substances including drugs, bee or wasp stings or by various foods [5-7]. Medical malpractice may occur with inappropriate treatment. In fatal cases, symptoms may be serious from the beginning, but delay both in diagnosis and in adrenaline administration are closely related to death (see below).

On the other hand, the false guidelines (recommendations for noradrenaline) issued in the 1970s are no longer seen in recent articles in medical journals and guidelines, and the use of adrenaline is recommended equivocally. This is appropriate.

However, Anaphylaxis Guidelines by the Japanese Society of Allergology [5] and the Guidelines by the World Allergy Organization (WAO) [6] have some inappropriate statements. It may result in delayed diagnosis or incorrect treatment. Therefore, we thoroughly and critically appraised these guidelines.

We hope that understanding the pathophysiology of anaphylaxis correctly by this article will lead to prompt diagnosis and appropriate treatment which will save the lives of patients.

What is anaphylaxis?

Anaphylaxis is a name of the disease given by Portier and Richet after they observed a phenomenon during their studies in 1902, using Actinia toxins instead of Physalia toxins. It was reported as follows: A healthy dog received a low dose of actinium toxin on day 0 and day 3, which was tolerated with 'almost no reaction'. After 22 days, he received the same dose when in excellent general condition. However, some seconds after the injections the dog began to gasp and to wheeze, the animal was agonized, was not able to stand and lay on his side, developed bloody vomiting and died within 25 min. [8]. This was a phenomenon in which a toxin worked reversely (ana-) to a defense (phylaxis), so it was named "anaphylaxis".

After that, this phenomenon was found to be a type I allergy caused by sensitization of dogs that were first inoculated with actinium toxin [9]. Of the four types of allergies, type I allergy produces IgE antibodies against the antigen in the body at the first inoculation, which binds to the second inoculated antigen, which stimulates mast cells to cause a reaction. Anaphylaxis is the most serious reaction of type I allergies.

Serious symptoms are due to mast cell degranulation.

Serious symptoms of anaphylaxis are basically caused by two mechanisms:

(1) Degranulation: Mast cells release granules containing inflammatory substances that have been stored in advance (symptoms appear immediately).

(2) New synthesized inflammatory substances are released (details will be described later).

Anaphylaxis is most often caused by type I allergic reactions, but this is not the only cause (**Note 1**). It can occur without allergies, but with chemical stimuli, non-allergic drug hypersensitivity (opioids, vancomycin, contrast media, disinfectants such as chlorhexidine, etc.), and even physical stimuli such as cold or abrasions caused by slipping accidents in the mountains [5-7].

Note 1: Severe attacks in some asthma patients due to hypersensitivity to non-steroidal anti-inflammatory drugs (NSAIDs) such as aspirin are not mediated by mast cells, but are sometimes included in anaphylaxis. It also occurs, very rarely, in type II allergies (cytotoxic) and type III allergies (immune complexes) that are not mediated by mast cells [10-12].

Symptoms of anaphylaxis

Regardless of the cause, the symptoms of anaphylaxis are basically due to the stimulants pre-formed and stored in the granules and the newly synthesised pro-inflammatory substances which are released by the activated mast cells. These points are particularly important which will be explained in detail later, because suppression of activated mast cells to stop degranulation and new production of pro-inflammatory substances is directly linked to rapid recovery from anaphylaxis (Note 1: mechanisms other than Aspirin/NSAIDs-induced asthma are extremely rare exceptions).

Histamine is the main stimulatory substance pre-formed and stored in the granules of mast cells. It causes anaphylaxis, but its half-life is as short as a few minutes [9], so if release of new granules is prevented, its effects will subside quickly.

On the other hand, leukotrienes and prostaglandins are newly produced pro-inflammatory substances in mast cells. This comes out about 5 to 30 minutes after the mast cells are stimulated. Cytokines such as TNF α and interleukin-4 (IL-4) are also produced on an hourly basis [9].

Mast cells are distributed throughout the body (submucosa and connective tissue), but the density of mast cell by organ varies individually. Those who are prone to atopic dermatitis, prone to pollen conjunctivitis, prone to pollen rhinitis, and those who are prone to bronchial asthma may have lot of mast cells in each organ. Migraine headaches are also related to the activation of brain and/or meningeal mast cells [13]. The symptoms of anaphylaxis also differ from person to person. This may also be related to the density of mast cells by organ of each person.

Symptoms of anaphylaxis need to be given special attention in the order of A, B, C.

A: Airway, B: Breathing, and C: Circulation, which are important in an emergency requiring resuscitation, also apply to symptoms of anaphylaxis [7] (Table 1).

(A) Airway

The most serious and life-threatening symptom is the obstruction of airway due to laryngeal edema. The larynx (the part with the vocal cords) is so narrow hence if it is swollen, the airways would be obstructed, resulting in serious hypoxia, loss of consciousness, convulsions, and shock. Shocks that occur by profound hypoxia are the most important cause of death from anaphylaxis.

In this condition, a patient stops breathing before complaining of respiratory symptoms such as dyspnea or wheeze [14,15]. These conditions occur without skin manifestations, so an inexperienced doctor may not know what happened. Blood pressure does not rise even if pressor agents were aggressively administered. Adrenaline should be used promptly (preferably slowly intravenously) in life threatening cases and tracheal intubated for oxygenation. Then you need a continuous infusion of adrenaline and corticosteroids. Moderate and mild airway symptoms include stridor (inspiratory laryngeal sound), changes in voice (wheezing = hoarseness) and stuffy throat.

(B) Breathing

Bronchial anaphylaxis causes coughing and wheezing (expiratory bronchial sound), dyspnea, tachypnea, hypoxic delirium, and cyanosis: those symptoms frequently observed in bronchial asthma attacks. As mentioned in (A) above, sudden respiratory arrest may occur

Table 1: Symptoms of anaphylaxis: ABC in order of seriousness

A. Airway: The most serious symptom is airway obstruction due to laryngeal edema.
B. Breathing: Bronchial breathing symptoms other than the laryngeal symptoms (wheezing, coughing, dyspnea, hypoxia, decreased SpO_2, etc.)
C. Circulation: decreased blood pressure, tachycardia, etc.
D. Derma (Skin/Mucous membranes): urticaria (hives), erythema, angioedema, pruritus with/without rash, prickle sensation, red and itchy eyes, numbness and flickering of the lips and fingertips
E. Entero-intestinal tract: diarrhea, abdominal pain, nausea, vomiting, etc.
F. Others
Brain: headache, dizziness, anxiety, behavioral changes, delirium, convulsions, unconsciousness
Heart: arrhythmia, myocardial ischemia, etc.
Any organs including bladder and uterus etc.

without apparent dyspnea or wheeze. Milder breathing/respiratory symptoms include rhinorrhea, sneezing, sore throat, etc.

(C) Circulation

When anaphylactic reactions occurs around a blood vessels, they may dilate, fluids exudate out of the blood vessel, blood pressure drops, and tachycardia occurs. However, severe dyspnea due to anaphylaxis may often rise blood pressure at early stage. This occurs because endogenous adrenaline is excreted in emergencies. But even in this situation with raised blood pressure, adrenaline is needed to treat anaphylaxis to stabilize activation of mast cells. Hesitation of adrenalin administration may worsen anaphylaxis.

(D) Derma / mucous membrane

Urticaria, rashes, itchiness, and redness occur on the skin and mucous membranes of the mouth or eyes. In sudden cases, only subjective symptoms such as numbness and flickering of the lips and fingers without apparent skin lesion may preceed.

(E) Entero-Intestine (digestive tract)

When it occurs in the digestive tract, it causes nausea, abdominal pain, diarrhea, and vomiting. Anaphylaxis caused by food or oral medication often causes swelling of the gastrointestinal mucosa, causing nausea and abdominal pain, followed by diarrhea, and then urticaria.

If the cause is food or oral medication, the first time only abdominal symptoms occur, the second time abdominal symptoms and urticaria may occur. In the third time, generalised urticaria and shock may occur due to anaphylaxis [13].

(F) Others

If it occurs in the brain, headache, dizziness, anxiety, behavioral changes, delirium, and in severe cases, convulsions and unconsciousness may occur.

Cardiac anaphylaxis may be manifested with arrhythmia or myocardial ischemia.

Anaphylaxis can occur in any organ, including the bladder and uterus.

Anyway, obstruction of the airways due to laryngeal edema is life-threatening and is the most important cause of death from anaphylaxis. Hypoxic shock requires oxygen. No matter how much the pressor agent is used, it is ineffective. Please be fully aware. In this regard, the guidelines are inadequate.

Adrenaline and corticosteroids are essential

It is the degranulation from activated mast cells that causes the symptoms of anaphylaxis. Even if you try to raise the blood pressure that was lowered by histamine, it will come out from the mast cells one after another. Therefore, symptoms of anaphylaxis will not subside unless supply of histamine, i.e. degranulation is shut off. How can degranulation from activated mast cells be suppressed?

The main player that suppress degranulation and activation of mast cell are adrenaline β_2 action and corticosteroids. Both receptors are present on the cytoplasmic membrane of mast cells.

Adrenaline acts on its β_2 receptor and suppresses mast cell activation and degranulation in seconds [16-18]. It not only suppresses the release of histamine, but also it suppresses new production and release of leukotrienes and prostaglandins [16,18].

Over the past decades, it was widely assumed that corticosteroids work solely through regulating gene expression, which needs several hours to take effect. However, it is revealed that corticosteroids have a second mechanism, termed rapid action that takes place within seconds to minutes after the exposure. This rapid action may involve plasma membrane and cytoplasmic activities of the corticosteroids receptor [19,20].

Adrenaline is, of course, essential for the treatment of anaphylaxis. But not only that, corticosteroids need to be used immediately. In the guidelines [5,6], this idea of "cutting off the source" is basically weak.

Noradrenaline has no β_2 effect and is ineffective

The α action (peripheral vasoconstriction) and β_1 action (enhancement of cardiac contractility) of adrenaline and noradrenaline are almost the same. If α and β_1 actions of adrenaline are important for treatment of anaphylaxis, noradrenaline should also work for anaphylaxis in cirtain extent. But in reality it is completely ineffective. Hence the β_2 action, which noradrenaline does not have, is essential for the treatment of anaphylaxis (**Figure 1**).

In this regard as well, the description of the Japanese and WAO anaphylaxis guidelines [5,6] are extremely vague.

Adrenaline after cardiac arrest is ineffective

The fact that adrenalin injection fails to improve the circulatory state in the situation where mast cell degranulation has almost completed [21-24] also shows the importance of "cutting off the source".

Death from anaphylaxis is due to the seriousness of the reaction itself occurring within minutes, in addition delayed adrenaline injection is crucial [22-24].

For example, if you hesitate to inject adrenaline because the patient's blood pressure is normal or even high in the early stages of anaphylaxis, patient's hypoxemia may progress and blood pressure may drop suddenly resulting cardiorespiratory arrest.

Adrenaline was used in treatment of 62% of fatal anaphylaxis but it was used before arrest in only 14%. [23,24]. Several other studies have been reported suggesting that delayed adrenaline use led to death [24].

Corticosteroids are also essential for anaphylaxis treatment

Another flaw in the guidelines is that they put little focus on the need of corticosteroid. Japanese guidelines describe "it takes several hours to develop action and may prevent biphasic anaphylaxis, but its effect has not been proven" [5]. WAO guidelines argue "Glucocorticosteroids are commonly used in anaphylaxis, with the objective of preventing protracted symptoms, in particular in patients with asthmatic symptoms, and also to prevent biphasic reactions (eg, intravenous hydrocortisone, or methylprednisolone). However, there is increasing evidence that glucocorticosteroids may be of no benefit in the acute management of anaphylaxis, and may even be harmful; their routine use is becoming controversial. " [6].

However, it takes only 30 minutes, rather than a few hours, for corticosteroid to bind to mast cell receptors and act on nuclear genes to suppress pro-inflammatory substances [19]. Moreover, it also acts on non-genetic receptors on the cytoplasmic membrane of mast cells to suppress degranulation in seconds or minutes [19,20].

Moreover and importantly, because when β_2 receptor resistance to adrenaline develop within a short period, namely one hour or so (Note 2), the effects of corticosteroid become stronger [16,25,26]. This mechanism works naturally in the human body. However, adrenaline and corticosteroid must be used to work properly against the special external stimulus of anaphylaxis.

> **Note 2:** In the event of a crisis, one responds by secreting adrenaline and dopamine, but continuous excitement and/or hard fighting causes ischemia in various parts of the body. Therefore, one reduces the number of receptors stimulated so that they do not continue to fight. This is called "down regulation". A 50-minute class and a 10-minute break (recently adopted at the university) is a reasonable way to prevent ischemic damage to the body due to sustained stress.

Evidence shows CS prevents biphasic reactions

Corticosteroid (CS) is underrated by not only in the Japanese guidelines [5] but also in the World Allergy Organization (WAO) guidelines [7] as above. However, we comprehensively analysed a review paper [27] that is one of the most important references that WAO guidelines cited and found that the data on a paper [28] which concluded that corticosteroids were meaningless indicated that no use of corticosteroid is related to increased risk with biphasic reaction clearly (Figure2).

Of the 240 extremely severe anaphylaxis cases in which patients were hospitalized for more than 8 hours after onset, corticosteroid was not used only in one case. Therefore, it is considered that the cause of the aggravation (or biphasic reaction) was something other than corticosteroid use or

Figure 1: Difference of actions and effects between adrenaline and noradrenaline

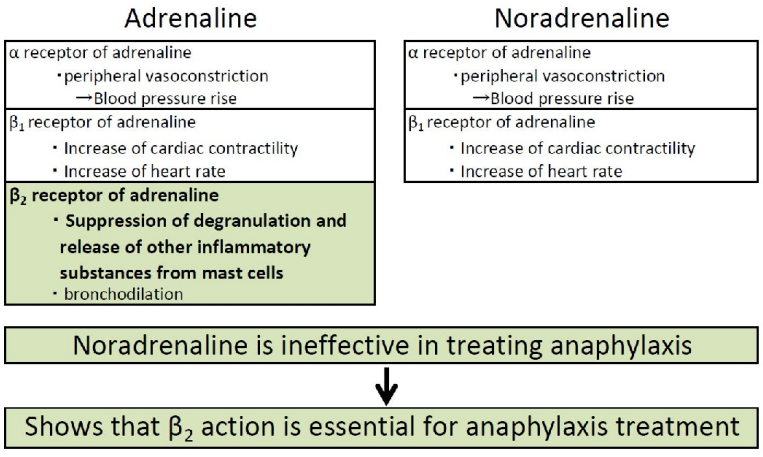
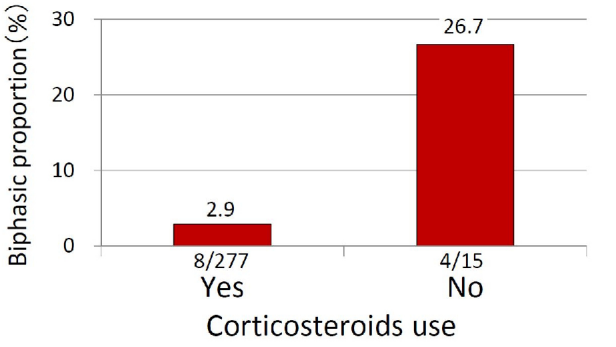


Figure 2:Corticosteroids prevent biphasic reaction of anaphylaxis

(Analysis of 292 anaphylaxis cases who were discharged within 8 hours)



Odds ratio = 12.2 (95% confidence interval: 3.2-46.8), p=0.000006

unuse (the cases were primarily serious).

On the other hand, of the 292 anaphylaxis patients who were discharged within 8 hours after the onset (which is considered to be relatively mild or moderate), 277 were on corticosteroid among which only 8 (3%) got worse again (biphasic). However, 4 (27%) of the 15 non-user of corticosteroids got worse again (biphasic). The risk of biphasic due to nonuse of corticosteroids was 12 times higher (**Figure2**).

No glucagon required

There are descriptions that glucagon can be useful to treat refractory anaphylaxis in a patient taking a beta-blocker [5-7]. This method is gaining worldwide recognition, but only two case reports [29,30] are the basis for the recommendation. In addition, we found 2 more cases [14,31] including a Japanese literature[14].

We examined these four cases in detail. First of all, it is noted that the β-blockers used were all cardiac-selective, that is, β_1-selective β-blockers in four cases. Atenolol in 2 cases [29,30], bisoprolol in 1 case [14] and metoprolol in 1 case [31]. Since these β_1-selective β-blockers do not inhibit β_2 action of adrenalin. Administered adrenalin can act on β_2 receptors on mast cell and shall be fully effective.

Second, careful examination of the treatment course of each case, revealed that the use (dose and infusion speed) of adrenaline was inappropriate in all 4 cases.

Three cases [14,29,30] had a decrease in blood pressure immediately after the use of contrast media. In one sudden case [14], cardiac arrest occurred only 2 minutes after administration of contrast media. In all three cases, intravenous bolus administration of adrenaline increased the blood pressure once. However, 2 cases [14,30] required 3 ampoules (1 mg x 3) intravenous bolus injection of adrenaline within 10 to 15 minutes. In one case [29], the pressor effect disappeared after 5 minutes.

The duration of the effect of bolus adrenaline is extremely short, within a few minutes, so continuous infusion is absolutely necessary in these cases (**Note 3** [32-35]). However, all three cases did not receive continuous infusion of adrenalin. In two cases [14,30], glucagon was used after continuously infused noradrenaline and dopamine which failed to treat (**Note 4** [36,37]) and blood pressure decreased again.

In one case [29], the blood pressure increased for 5 to 10 seconds to 80/50 mmHg and heart rate increased transiently to 60 /min after intravenous injection of 1 mL of adrenaline (1:10,000) and intravenous saline. So it was effective. However, when the patient failed to respond to adrenalin within 5 minutes, reason of short duration of effect of adrenalin was mistakenly considered the concomitant use of beta-blocker (atenolol), a 1 mg intravenous bolus glucagon was given and mean arterial blood pressure increased from 55 to 75 mmHg. He received another 1mg bolus glucagon but blood pressure decreased again after 30 minutes. Then he was given continuous intravenous infusion of glucagon. He was also given intravenous methylprednisolon 125 mg every 6 hours and diphenhydramine 50 mg intramuscularly.

In these cases sufficient continuous infusion of adrenaline shall be surely effective. But in these cases no or insufficient continuous infusion of adrenaline was used. Treatment failure with adrenalin in these anaphylaxis cases is not surprising.

Another case [31] was a 54-year-old woman who had anaphylaxis induced by the anti-interleukin-5 monoclonal antibody mepolizumab for bronchial asthma. After intramuscular injection of 0.3 mg of adrenaline three times and intravenous injection of 125 mg of methylprednisolone, blood pressure finally improved to 186/118 and heart rate 77/min. However, glucagon was used because she continued to feel that her throat was closing and other medication review revealed that she was on metprolol treatment, although she was saturating 96% on room air.

Mepolizumab is an extremely long acting drug with a peak blood concentration of 2 to 3 hours after

intravenous injection, 5 days for subcutaneous injection, and a half-life of around 20 days (according to a Japanese package insert).

Therefore, it is considered that the anaphylactic symptoms continued, as antigen stimulation persisted with feeling of obstruction of the larynx. Both blood pressure and heart rate were completely recovered (blood pressure 186/118) and no adverse effect of β-blockers was seen when glucagon was given.

In summary, all four cases in which anaphylaxis was intractable due to the use of β-blockers were only intractable due to inappropriate use of adrenaline and corticosteroids. With proper use of adrenaline and corticosteroid (**Note 4**), glucagon is absolutely unnecessary.

Note 3: The duration of effect of isoprenaline is about 3 minutes [32], and the duration of effect of adrenaline is shorter than isoprenaline [33]. In anaphylaxis, intramuscular injection of adrenaline has a peak effect after 5 to 10 minutes and lasts for about 40 minutes [5,34]. However, from the results of animal experiments, in super-severe cases of sudden cardiac arrest, neither intramuscular nor subcutaneous injection are effective, and the effect of one intravenous injection is temporary and ineffective without continuous infusion. [35].

Note 4: In the cases in reference [14], adrenaline was continuously infused after three bolus intravenous administration, but it was 0.02 to 0.08 μg/kg/min, which is extremely low compared with the recommended dose for severe cases (0.3 to 0.45 μg/kg/min) [36,37]. In any case, the use of adrenaline was inappropriate. In this case, corticosteroid were not used for at least 2 hours after the onset, and it is assumed that the timing of glucagon injection coincided with the timing of the commencement of effectiveness of delayed use of corticosteroid.

Glucagon is merely an adjunct to beta-blocker overdose

Glucagon acts on a site different from adrenaline to increase c-AMP, which is the source of energy in the cell, acts like adrenaline, and also acts on mast cells, vascular smooth muscle, and myocardium [38]. However, even in the case of overdose of beta-blocker, the basic treatments are adrenaline, isoprenaline, and vasopressin, and glucagon has only a supplementary meaning [39].

Moreover, non-toxic doses of beta-blockers, especially β_1-selective beta-blockers, do not antagonize the β_2 action of adrenaline, so if adrenaline and corticosteroids are properly used, glucagon is not needed at all.

Adrenaline while using antipsychotics

Adrenaline was previously contraindicated in combination with neuroleptics (antipsychotics) such as haloperidol and risperidone, but recently it is no longer contraindicated in the case of anaphylaxis [40].

Adrenaline is still contraindicated for overdose of antipsychotics with circulatory collapsed shock. In fact, some cases were reported [41,42]. The mechanisms are summarized that large amounts of neuroleptics antagonize the α action of adrenaline, and the β_2 action of adrenaline causes the blood vessels in the muscles to dilate and to decrease blood pressure. In this case, noradrenaline, which has no β_2 action should be used to increase blood pressure.

Noradrenaline is ineffective for treatment of anaphylaxis developed in a person taking recommended doses of antipsychotics. Adrenaline is absolutely needed, and it is unlikely to cause a paradoxical decrease in blood pressure in a patient treated with recommended dose of neuroleptics. However, in very rare condition in which airway is no longer obstructed, there is no difficulty breathing, and only recovery of blood pressure is poor, noradrenaline might be necessary.

In practice

The principles of treatment for anaphylaxis are shown in Table 2 with some modifications to the UK guidelines [8,43].

Anaphylaxis is a serious adverse reaction caused by drugs. Inappropriate treatment may not save lives, but proper treatment can prevent death.

Diagnose anaphylaxis appropriately as soon as possible, inject adrenaline immediately, and remember to use corticosteroids subsequently.

Table 2: Principles of anaphylaxis treatment

1) Discontinue the causative agents (If during infusion, stop and remove it or change to saline solution leaving only the indwelling needle/catheter)
2) Gather medical staff for treatment
3) Adrenaline intramuscularly : ・ Adult: 0.3-0.5 mg (on the outside of the thigh) ・ Children: 0.01 mg / kg (upper limit 0.3 mg, diluted for low body weight)
4-6) ・ Horizontally raise your legs in the supine position (in the lateral decubitus position when vomiting) ・ After securing the venous route, fluid replacement ・ Sufficient oxygen inhalation (considering tracheal intubation and artificial ventilation)
7) Corticosteroids: Intravenous injection of hydrocortisone 200 mg * (corresponding dose for children)
If the aboves are used promptly, anaphylaxis is rarely aggravated. However, in the life threatening cases with already seriously hypoxic and/or hypotension when a doctor see the patient, administer
8) 5 mL out of a total 10 mL (Adrenaline 1 mg (1 mL) + saline 9 mL) intravenously in about 1 minute, and adrenaline should be intravenously infused **(recommended dose for life threatening cases is 0.3 to 0.45 μg/kg/min).** If the venous route is not available, intramuscular 0.3 to 0.5 mg (0.3 to 0.5 mL) at 3 to 5 minute intervals can be used.

Modified from ref. [8]

*: However, for patients with a history of aspirin/NSAIDs-induced asthma, oral prednisolone 50 mg or betamethasone injection 4-8 mg should be selected, because these are not a succinate ester and does not contain parabens (methyl paraben or propyl paraben).

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Vaccines for COVID-19

High incidence of anaphylaxis: 1 in 4400 vaccinated

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Med Check Editorial Team

Abstract

- The Ministry of Health, Labor and Welfare (MHLW) said that out of 181 reported anaphylaxis cases after about 580,000 doses, only 47 met the diagnostic criteria and that there was no serious concern.
- However, according to our careful examination, there were 132 anaphylaxis cases which are clinically diagnosed out of 181 (73%). The incidence of anaphylaxis was calculated as 230 per million doses, or about 1 in 4,400.
- Reported incidences of 5 and 20 per million doses in the United States and Europe respectively are, based on the spontaneous reports. Hence they are extremely inaccurate. In fact, in the United States, a precise survey shows that the incidence is as high as 230 to 270 per million times (1 in 4000).
- Considering that healthy people receive the vaccine, it should be said that the incidence is extremely high.

Keywords:
anaphylaxis, Brighton criteria, adrenaline, Epipen, polyethylene glycol, bronchial spasm, laryngeal edema

Introduction

The Ministry of Health, Labor and Welfare (MHLW) announced on March 12, 2021 that it had received 36 anaphylaxis case reports [1] and on March 26 that a total of 181 anaphylaxis case reports with approximately 580,000 vaccinations by March 21[2]. As a result of experts' assessments by applying the Brighton Collaboration case definition [3], which is widely used in the diagnosis of anaphylaxis, 47 out of 181 reported cases (26%) met the definition, or 81 per million doses. Therefore, they judged that "no serious concern was found" [4]. Here we report the results of our careful assessment of these reported cases.

Characteristics of 181 cases reported

Age distribution of 181 cases was as follows: 33% was in their 40s, around 20% was in their 20s, 30s, and 50s, and 3% was in their 60s. Only 8 were males (4.4%) and 173 (95.6%) were females. The proportion of female among health workers including doctors, pharmacists [5] and nurses [6] based on the statistics of MHLW in 2018 was 77% (1.7 million among 2.2 million in total). Compared with the proportion, 95.6% is significantly high ($p<0.00001$).

The vaccine contains a lipid nano-particle to prevent degradation of mRNA. It is polyethylene glycol (PEG) which is also contained in many cosmetics or personal care products etc. [7], Women who use cosmetics are more easily sensitized and develop allergy to lipid PEG. It seems that this is one of the most important causes why the proportion of females is high among those with anaphylaxis.

Among 181 cases, 125 (69%) had some kind of hypersensitivity, and of the 125 people, 36 (nearly 30%) had a history of asthma. There were 17 (14%) people who had experienced anaphylaxis in the past.

Clinical anaphylaxis cases were 132

According to our assessment by applying the Brighton

Collaboration case definition to the 181 reported cases, 81 (45%) met the definition. The Brighton definition often excludes some clinically important anaphylaxis cases as shown later in this article including extremely serious cases, or those in which adrenalin etc. was used at a very early stage and subsequently other symptoms did not appear. We included these cases as anaphylaxis in addition to cases identified by the Brighton case definition. As a result, 132 cases (73%) were classified as anaphylaxis.

Incidence of anaphylaxis is 230 per 1 million dose (132/580,000) or about 1 in 4400 doses.

Same incidence as the rigorous US survey

Very low incidences of anaphylaxis, 5 or 20 anaphylaxis per 1 million doses in the United States and in Europe [1,2] are based on the spontaneous reports and are extremely inaccurate.

A rigorous survey of healthcare professionals in the United States [8] reported anaphylaxis in 270 per million doses with the Pfizer vaccine and 230 per million doses with the Moderna vaccine. Both are about 1 in 4000 people. These results in the United States are very close to that in Japan, so it is certain that the anaphylaxis is very frequently occurring in the world.

Cases excluded from anaphylaxis by the authorities

Among the cases [2] excluded from anaphylaxis cases by expert examination, two largely questionable cases are shown (for other problematic cases, refer to the rapid report No191 [9] and No194 [10]).

Case 42:

A 26-year-old woman with a history of anaphylaxis induced by crabs and pineapples. Epipen (a portable adrenaline injection) is prescribed.

The vaccine (Pfizer/Biontec) was injected intramuscularly, and 5 minutes later, nasal discharge and cough appeared. Dyspnea occurred and worsened immediately with remarkable airway obstruction symptoms. Adrenaline was injected intramuscularly, four doses in total. In addition, she was treated with corticosteroids and antihistamines. She subsequently recovered but she was hospitalized for follow-up observation.

Expert's assessment: Brighton classification: Category 4 (Reported anaphylaxis with insufficient evidence to meet the case definition)

Expert's comments: It is not a case of anaphylaxis because only respiratory symptoms were reported.

Comments by MedCheck：Symptoms appeared about 5 minutes after vaccination. Hence it meets the first criteria of diagnosis of anaphylaxis **(1)** sudden onset. Moreover, dyspnea with sign of airway stenosis is prominent with rapid progression: **(2)** signs and symptoms at a very early stage. Four doses of intramuscular injections of adrenaline indicate the severity of this case.

Criterion **(3)** the symptoms in two or more organs was not met. Therefore in spite of severe anaphylaxis, it was classified as Category 5 (Not a case of anaphylaxis) by the Brighton classification.

However, she has a history of anaphylaxis. If a doctor had waited without treating her with adrenaline until some urticaria or other skin symptoms appear, she might have been deteriorated with airway obstruction. Hence it was absolutely appropriate that the doctor decided to administer adrenaline before skin reactions appeared. This is one of the most excellent examples showing a defect in the Brighton case definition.

If applied to the latest WAO guidelines：Because a serious and definite anaphylaxis case might be excluded by the former criteria and/or Brighton case definition, the latest guidelines of the World Allergy Organization (WAO) issued in 2020 [8] revised their diagnostic criteria and added an item as follows:

Acute onset of hypotension or **bronchospasm** or **laryngeal involvement** after exposure to a known or highly probable allergen for that patient (minutes to several hours), **even in the absence of typical skin involvement.**

If this new criterion is applied, the case 42 is definitely anaphylaxis. Hesitating to inject adrenaline due to the absence of skin lesions may have led to hypoxic shock with cardiopulmonary arrest and death. The revised criterion is extremely important.

Case 13:

A 53-year-old woman with a history of hypertension

and hyperlipidemia.

About 15 minutes after vaccination, precordial redness with rash and dyspnea occurred. A sound of upper airway stenosis was heard. Adrenalin was injected intramuscularly and symptoms improved. A histamin H1 antagonist, a H2-blocker and an intravenous corticosteroid were administered subsequently. After a follow-up for a while and recovery was confirmed, she was discharged.

Expert's assessment: Brighton case definition：**Category 4**

Expert's comments: Each symptom is not clear enough for diagnosis as anaphylaxis.

Comments by MedCheck：The sound of upper airway stenosis is called "stridor" which indicates that the patient has laryngeal edema, one of the most important symptoms leading to death without appropriate treatment, i.e. immediate administration of adrenaline. Hence it is one of the major respiratory symptoms of the Brighton case definition. Precordial redness with rash is at least one of the minor criteria on the skin. Therefore, it can be judged as **Category 2 (level 2)** by the Brighton case definition. It is not understandable why the experts excluded this case from anaphylaxis by applying the Brighton case definition.

Conclusion

People who have some problems such as fever or headache on the day of inoculation will not receive the vaccine. In other words, a healthy person who is in good physical condition at least on that day can receive the vaccine.

Considering these, the incidence of 1 in 4400 as shown in this article is extremely high. It must be said that the incidence of anaphylaxis is too high compared with the benefit.

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