Part 1 – Clinical Dentistry of Implants

Chapter 1- Drugs used in implant treatments

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I. Tranquilizers

The general perception of the use of tranquilizers may be for its use in psychological disorders, but in the field of dentistry, it is an agent that is administered as a preanesthetic or for sedative purposes, as will be mentioned in this book (Refer to The Fundamentals chapter, p. 123-126 for details). Preanesthetics are the sedative agents that are taken before inducing a general sedative to reduce the anxiety of patients, restrain respiratory secretion, prevent adverse reflects, and also to prevent the fall in analgesia levels and body metabolism. Anxiety and nervousness is often felt by the patient prior to surgery, therefore administration of pharmaceutical agents that are mentioned below should be considered. It is important to note that the effects of these agents can induce strong signs of drowsiness and dizziness – which the patient should be informed at consultation since these are required to be taken an hour prior to surgery. Additionally, these agents are known for their anticonvulsant effects, therefore are also administered for hyperventilation syndromes, local anesthetic poisoning, and for epileptic fits. If administering via the intravenous route, respiratory control must be taken into account.

A. Benzodiazepines

1. Diazepam

This has been used as both via the intravenous or as preanesthetics for a long time, and is known for its safe usage. Common brand names such as Cercine[®], Horizon[®] are induced as intravenous sedation 0.2 to 0.4 mg/kg via the intravenous route. The downside of this is that angialgia or vasculitis (the pain or inflammation felt in the veins from the administration of the drug) can also be induced. As preanesthetics, 2 to 10 mg should be administered.

2. Midazolam

It is used as an intravenous sedation agent that has become increasingly administered due to its shorter duration of action compared to diazepam. Dormicum[®], 0.05 to 0.075 mg/kg is commonly administered intravenously. The simplest method is to dilute the ampoule formulations made as 10 mg in 2ml (i.e. 5mg/ml) using distilled water for injections, or biological saline to 1mg/ml (5 time dilution) or 0.5mg/ml (10 times dilution).

3. Flunitrazepam

The duration of action is longer than that of diazepam, and is often used for a relatively long term treatment. Doses of 0.01 to 0.015 mg/kg of Rohypnol[®], or Silece[®] are injected gently into the veins. As with the midazolam, it is easier to administer by dilution. Its tablet forms have been used for sleep inducers, and if 1mg of this are often administered as preanesthetics, to reduce any anxiety, or nervousness felt by the patients.

4. Traizolam

Halcion[®] is administered as a sleep inducing agent. This option is considered if sleeplessness, due to anxiety can be expected on the day before surgery.

5. Alprazolam

To ease anxiety or tension felt by the patient, with the brand name of Solanax[®]. Best effects can be expected with administration of 0.4 mg (one tab) two hours before surgery.

6. Lorazepam

Conditions of anxiety can be eliminated with agents such as Wypax[®], and are often used as preanesthetics. Also prescribed for panic disorder, a dose of 1-3 mg is administered per day for this condition.

B. Barbiturates derivatives

There are a number of types for this group, thiopental, thiamilal (short action), pentobarbital (short action), amobarbital (medium action), and phenobarbital (long action) and are further divided by their duration of action. Rapid acting, and short acting agents are applied as intravenous sedation or intravenous analgesia in preparation for the induction of general anesthesia, and the medium, and long acting agents are used as preanesthetics or anticovulsant agents.

When administering these agents for intravenous sedation, the dose should be determined with a close watch of patient conditions, alongside this, monitoring their blood pressure, heart rate, and respiratory conditions are strongly recommended. In particular, any restraints can be detected readily by pulse oxymetry, SpO₂.

II. Sedatives (Table 1-1-1)

Essentially, the signal of pain is a warning sign that should not be ignored but the source of the warning should be investigated. In implant surgery, the large source of pain is usually caused by the surgical invasion, therefore analgesic agents for pain control are taken in order to prevent any physiological effects that could result from a large pain.

Narcotic analgesic		
Antipyretic analgesic	Salicylic acid derivative	Sodium salicylate
		Methyl salicylate
		Acetylsalicylic acid
	Anilines	

Table 1-1-1 Classification of analgesics

A. Narcotic analgesics

As morphine as a classic example, narcotics are a group of agents that are effective for pain relief. Others include, codeine, pentazocine, fentanyl and used for various effects. However, the uses of these agents require strict management, therefore are not used in implant surgery.

B. Antipyretic analgesics

1. Salicylic acid derivatives

Well known as the non-sterioidal anti-inflammatory drugs (NSAIDs), there are sodium salicylic acid, methyl salicylate, acetyl salicylate, and the typical uses involve agents such as aspirin, and acetyl salicylate as ethenzamide. They also have antipyretic actions which are effective in the reduction of temperature under high temperatures, but have no effect under normal conditions. However its analgesic effect is less than that of the narcotics, and is not effective for visceral pains. The main side-effects include those of the digestive tract such as nausea, vomiting, and can result in stomach ulcers.

2. Aniline derivatives

Acetoaminophen (Calonal[®]) as a typical example, it has antipyretic effect, but no anti-inflammatory actions. Contrary to NSAIDs, it has the advantage of hardly having side-effects to the digestive systems.

III. Anti-inflammatories (Table 1-1-2)

Inflammation, with pain have been regarded as physiological defense mechanism, and five symptoms, redness, pyrexia, inflammation, swelling, and dysfunctions have been advocated from the past. Anti-inflammatory agents are often administered to prevent these symptoms becoming extreme.

	Steroidal anti-inflammatory drugs	
Nonspecific anti-inflammatory drugs	Nonsteroidal anti-inflammatory drugs	Acidic non-steroidal anti-inflammatory drugs Non-acidic non-steroidal anti-inflammatory drugs
	Oxygen-inflammatory drugs	
Specific		
anti-inflammatory		
drugs		

Table 1-1-2 Classification of anti-inflammatory drugs

A. Non-typical anti-inflammatories

1. Steroidal anti-inflammatories

Glucocorticoids within the steroid hormone family have strong anti-inflammatory effect, and hydrocortisone, prednisolone, triamcinolone, dexamethasone are present. It is often administered systemically against serious allergic reactions in those with autoimmune disorders and cases of anaphylactic shock. Triamcinolone and dexamethasone can be administered intraorally as ointments. Although an effective agent as anti-inflammatory agents, its effectiveness can lead to serious withdrawal symptoms such as, muscle and joint pain, nausea and vomiting, and hypotension, and side-effects such as osteoporosis, diabetes, aggravation of infection, and stomach ulcers. Therefore a long-term administration should be done with extreme caution.

2. Non-steroidal anti-inflammatories

NSAIDs, as mentioned above, also have analgesic and antipyretic effects, therefore are effective in the field of dental surgery for the infectious anti-inflammatory effect, postoperative inflammatory control, for pain, and non-infectious anti-inflammatory.

a. Acidic non-steroidal anti-inflammatories

Typically used as the main substituent of aspirin, mefanamic acid, indomethacin, diclofenac sodium, ibuprofen, Loxoprofen sodium, Ampiroxicam are also included in this category. Side-effects that may arise are, gastrointestinal effects, sensitivity, renal/ hepatic failure, blood dyscrasia or hematologic disorder, and disorder of the central nervous system. The most common amongst these are those affecting the gastrointestinal tract, which can progress onto stomach or duodenal ulcer.

b. Non-acidic non-steroidal anti-inflammatories

3. Enzymatic anti-inflammatories

Enzymatic agents such as serratiopeptidase, pronase, lysozyme chloride, streptokinase do not have analgesic or antipyretic effects. However, they are applied for effects such as, vascular permeability, restrain formation of oedema or granulation tissues, and promote mucus discharge and migration of the site of inflammation.

B. Typical anti-inflammatories

These involve antirheumatic drugs for chronic arthritis conditions and immunosuppressants for treatment of gout are in this category. Therefore are not used in implant surgery.

IV. Chemotherapy (Antibacterials) (Table 1-1-3)

The term, chemotherapy are used mainly for treatment of malignant tumour, or infection. As implant treatment does not deal with malignant tumour conditions, we will only mention the drugs for infections. The term antibiotics used to describe any substance produced by a microorganism that was effective in inhibiting the growth of another in high dilution were included in the term, however, with the advances in medicinal chemistry, the term antibacterial is used as a synonymous term that also encompasses chemically synthesized materials.

The interior of oral cavity acts as an optimum environment for growth of microorganisms, therefore in implant surgery, an intraoperative use of antibacterials are common.

There are no antibacterial agents that are effective for a whole spectrum of microbes and are specific to the effective agents. This is called the antibacterial spectrum. Therefore it is essential to select the agents having established the causative agents.

A. β -lactam antibiotics

1. Penicillins

Natural penicillin was the first antibiotic that was discovered, but because of its overuse, resistances have been developed in a significant number of organisms, therefore are no longer common. Semi-synthetic, narrow spectrum antibiotics including methicillins and oxacillins are effective for Gram positive bacteria, in contrast, the broad spectrum antibiotics, ampicillin, amoxicillin, bacampicillin are effective also for Gram negative bacteria. Additionally, sulbenicillin, piperacillin, and carbenicillin are effective against *Pseudomonas aeruginosa*.

2. Cephalosporins

This class is divided into four groups depending on their "generations" or period of discovery. First generations include cephaclor and cephalexim and show effectiveness against broad spectrum of microorganisms including, gram positive coccus, and *Klebsiella pneumoniae*. Second generation agents such as cefaloxime and cefotiam are more effective against the gram negative bacteria than the first generation agents. Cefoxitam and cefixime are the third generation agents, and cover a broader spectrum of efficacy against gram negative bacteria than the second generation. The fourth generation that involve, cefpirome and cefepime are effective against *Staphylococcus aureus* and *P. aeruginosa* on top of the other bacteria.

	Penicillin
	Cefem
β - Lactam antibiotics	Carbapenem
	Penem
	Monobactam
Aminoglycoside antibiotic	
Macrolide antibiotic	
Tetracyclines	
Pyridon carboxylic acid	
synthetic (Quinolone) antibacterial agent	

Table 1-1-4 Chemotherapy drugs (antibiotics)

3. Carbapenems, penems, monobactams

The three types, Imipenem, Panipenem, Meropenem are under carbapenems, which have a broad spectrum of activity, against gram positive, gram negative, as well as anaerobic bacteria.

Penems show a strong activity against gram positive and negative agents, excluding *P. aeruginosa*. Monobactams are effective against gram negative agents including *P. aeruginosa*, as well as the influenza viruses.

B. Aminoglycoside

Included in this group are kanamycin, amikamycin, tobramycin, gentamycin, and arbekacin. These display activity against gram positive and negative bacteria as well as *Mycobacterium tuberculosis* and *P. aeruginosa*. Arbekacin, amongst these, is also effective against methicillin-resistant Staphylococcus aureus (MRSA).

C. Macrolides

This group of agents is effective against broad spectrum of microorganisms such as, gram negative bacteria including staphylococci, or gram positives such as gonococci, spirochete, mycoplasma, rickettsia, and chlamydia. Erythromycin, roxithromycin, chlarithromycin, telithromycin, azithromycin and rokitamycin are in this group. In comparison to the other agents, the absorption from the digestinal tract is much better, therefore are often orally administered.

D. Tetracyclines

Effective against the gram negative and positive bacteria, mycoplasma, rickttsia, chlamydia. The agents include, chlortetracycline, tetracycline, methacycline, doxycycline, and minocycline. Although commonly administered orally, it is in the form as ointments, lozenges, or as a local filling agent in some settings.

E. Synthetic pyridonecarboxylic acid (Quinolone)

These include, ciprofloxacin, ofloxacin, and levofloxacin, and are referred to as third generation new quinolone. Its use has become more common due to its low frequencies of side-effects occuring. The agents are readily absorbed from the digestive tract, therefore are often administered as oral medicines.

If the above chemotherapeutic agents (anti-bacterials) are administered repetitively, or if the administered dose or the administration period is insufficient, the microorganisms can gain resistance against the agents, therefore reducing the pharmacological effect or become ineffective. This is referred to as 'antibiotics resistance', and the microorganisms, 'antibiotic resistant bacteria'. Furthermore, if the microorganism becomes resistant to one kind of agent, these can also be resistant to the agents of the same types, which are referred to as cross-resistance. The resistance and cross-resistance have become a major problem in Japan in the recent years; therefore, more careful considerations should be given in administration of these agents.

As the main side-effects of chemotherapeutic agents, the disorder of organs including bone marrow, liver, kidneys digestive tracts, sensory organs, nervous systems, and allergies, and skin diseases are common. In particular, the liver or kidney failures, and serious allergic reactions like anaphylaxic shock that arise as a result of long-term administration have to be taken into consideration when choosing the agents.

V. Anticoagulants

This group can be divided into systemic and local agents. Under usual implant surgery, the local anticoagulants are most commonly administered. Though, systemic anticoagulant can be adopted in extremely rare cases of unexpected bleeding.

A. Systemic anticoagulants

1. Vitamin K

Vitamin K is involved in the synthesis of coagulation factors, and agents such as phytonadione (K1) and menatetronone (K2) are used in case of deficiency, however, it not an emergency.

2. Blood products

Applied in the cases of inherent shortage of coagulation factors. For example, in the case of haemophilia A, Factor VIII preparations, or for haemophilia B, Factor IX preparations or platelet concentrate preparations are administered.

3. Antifibrolytic agents

The agents for this are known as anti-plasmin drugs, and the examples include, epsilon-aminoacaproic acid, Tranexamic acid as typical agents in use.

4. Capillary stabilizer

Adrenochrome preparations including carbazochrome, ascorbic acid (vitamin C), flavonoids are used.

B. Local anticoagulants

1. Thrombin

It can be applied topically for controlling bleeding from capillaries and small venules. Thrombin is one of the physiological coagulation factors. As it requires fibrinogen for coagulation to occur, in the patients suffering from hypofibrinogenemia, application of this agent is ineffective.

2. Absorbable gelatin sponge

This can absorb a large volume of blood for a physical antihemorrhagic effect by forming a mesh by effervescence of the gelatin solution. In addition, as this activates the platelets, rapid blood coagulation can be expected. There are no irritative, impairing or antigenic effects to the tissues, and are absorbed within a month.

3. Oxidized cellulose

By expansion mechanisms, the flexible and absorbable fibres act to absorb large volumes of blood. It can be applied to the bleeding site, for an antihemorrhagic effect. It has been reported that it is absorbed within one to three weeks, but due to its acidity, processes such as osteogenesis and wound healing can be delayed.

4. Astringents

Aluminum chloride preparations are effective for small scale bleeding by acting astringently in the blood vessels.

5. Adrenaline

It has a strong constricting effect on the peripheral blood vessels therefore are often included in the local anesthetics as antihemorrhagic, or to stop bleeding in a large area, the diluted solution is used to soak the gauze for application.

	Vitamin K
Systemic hemostatic agent	Blood products
	Antifibrolytic agent
	Capillary stabilizer
	Thrombin
Local hemostatic agent	Gelatin sponge
	Oxycellulose
	Astringent drug
	Adrenalin

Table 1-1-4 Haemostatic agents

VI. Mouthwash

A. Fluoride rinsing agent

Either rinse once a day with 0.05% sodium fluoride solution, or once a week or once every two weeks with a 0.2% solution for prevention of tooth decay.

B. Azulene sodium sulfonate, povidone iodine, benzethonium chloride

Used for all types of stomatitis. Consider diluting the agent if any symptom of pain arises.

VII. Local anesthetics

Local anesthesia is imperative for implant treatment. As mentioned previously, a number of local anesthetics contain adrenaline or felypressin as vasoconstricting agents, therefore it should be noted of the systemic effect of these agents.

A. Surface anesthetics

1. Lidocaine

This is a commonly administered amide local anesthetics in the field of dentistry. As the surface anesthetics agents are supplied in the forms of jelly (2%), viscous (2%), or as spray (8%). Although there are no applications to the oral cavity, tapes that contain 60% lidocaine are also formulated. These are all administered to relive the pain from injecting infiltration or conduction anesthesia.

2. Benzocaine (ethylamino benzoate)

This agent is used as 5 to 10 % formulation for surface anesthetics due to its low water solubility.

3. Tetracaine

A small sponge is soaked in the 6% solution, and surface anesthesia is expected when applied to the mucosal membrane.

B. Infiltration, conduction anesthesia

1. Lidocaine

This is the standard amide local anesthetics. As infiltration and conduction anesthesia, typically, 2% lidocaine solution, with roughly 1/80,000 adrenaline as an adjunct for vasoconstriction is used. Widely applied in the field of dentistry for its rapid infiltration, it is supplied as a glass tube that is referred to as cartilage, to enable application with high pressure. Lidocaine inhibits irritatability to the myocardium, therefore are also used as antiarrhythmic agent.

2. Prilocaine (propitocaine)

This has low lipid-solubility therefore is an amide anesthesia that has less or equal efficacy as lidocaine, but are slower onset of action. 3% concentration solution is often used. However, its toxicity is lower than lidocaine, and does not have problems of accumulation. Dosages of over 600 mg can induce methohemoglobinemia (a condition in which the haemoglobins are converted into methohaemoglobins that has inferior oxygen carrying abilities). Typically, the cartilage formulations containing felypressin as adjuct vasoconstrictors are distributed.

3. Mepivacaine

This has similar anesthesic effect, onset time, and duration of action to lidocaine. However, in contrast to the vasodilatation action of lidocaine, it has a slight vasoconstriction effect, dental cartilages without the vasoconstrictor adjuncts are in supply. With no systemic vasoconstricting effect and no additives, it is regarded as a safe agent with that is suitable for induction to a low scale treatment where a rapid infiltration is required.

A. Oxidizing agent

Both Oxydol (3% hydrogen peroxide containing solution) and potassium permanganate (0.2 to 1% solution) act as mechanical cleaner or disinfectants by the generation of oxygen bubbles.

B. Halogen containing compounds

1. Chlorine, chloride compounds

Sodium hypochlorite are effective against bacteria, *P. aeruginosa*, fungi, and viruses, and are administered as 0.01 to 0.5% disinfectant to the fingers, skin and in the surgical areas, and as 3 to 10% for treatment of root canal (dental antiformin, hypochlorite, Neocleaner). In addition to the antibacterial action, the sodium hydroxide can dissolve the tissues, therefore special care must be taken to inhibit any leaking out of the root canal.

There are two forms for chlorhexidins, chlorhexidine chloride, and chlorhexidine gluconate that are effective against gram positive and negative, but have no activity against bacterial spores or viruses. Chlorhexidine chloride, often in the form of lozenges, are used to prevent infection of intraoral wounds. Meanwhile, the chlorhexidine gluconate are often used as 0.1 to 0.5% concentrations for disinfection of fingers, skin, surgical areas, and disinfectants of apparatuses. 1% solutions had frequently been used previously, however due to reports of shock symptoms when applied to the mucosal membrane, the uses of higher concentrations have been forbidden.

2. Iodine, iodide compounds

There are: iodine tincture, iodine glycerin, iodine iodoform, povidone iodine as the different forms.

Alashala	Ethanol (Ethyl alcohol)
Alcohols	Isopropyl alcohol (Isopropanol)
	Formaldehyde
Aldehydes	Paraformaldehyde
	Glutaraldehyde (Glutaral)
	Phenol
Phenol	Cresol
	Parachlorophenol
	Cationicsurfactants
Surfactant	Anionic surfactants
(Surface-active agent)	Amphoteric surfactants
	Nonionic surfactant
Organia dua	Acrinol
Organic dye	Methylrosanilinium chloride



C. Alcohols

There are ethanol (ethyl alcohol) and isopropyl alcohol (isopropanol) which are effective for Gram positive and negative bacteria and HIV, but not for spores and virus. 70% ethanol or 50 to 70% isopropyl solutions

are used to disinfect the finger tips, skin, surgical area, and medical apparatus.

D. Aldehydes

There are formaldehyde, paraformaldehyde and glutaraldehyde (glutaral), which have bacteriocidal activity whereby the proteins of the microorganisms are denatured. Formaldehyde has a strong stimulant action, therefore are included in the formulations for the drugs used in disinfection of the root canal, pulp capping, and root canal obturation. When paraformaldehyde is applied onto the dental pulp, it can produce aldehyde gas, therefore require a disinfection that is continuous and one that is highly permeable. Glutaraldehyde is effective for spores, virus, and fungi, but due to its irritating nature on the skin, its application to the biological body is avoided. Instead, these are used to sterilize the apparatus. It shows effectiveness especially for those suspected of being infected with Hepatits B virus or HIV.

E. Phenols

There are phenol, cresol, para-chlorophenol under this group. Due to its irritative nature, phenols are no longer used as the disinfectant on the finger tips, and skin, but are used in combination with volatile oil (camphor) for the disinfection of the cavity, root canal or as analgesics, sedation of the dental pulp. Cresol is used as formocresol in a formulation with liquid soap, or with formalin for the disinfecting agent of the finger tips and skin, or for root canal, respectively. para-chlorophenol is used in a formulation with camphor for infected root canal.

F. Surfactants

There are cationic, anionic, or non-ionic surfactant types. Cationic agents include general soap and detergents, with its strength to lie in the washing power, with no effectiveness as a disinfecting agent. On the contrary, the anionic agents, also known as invert soap, where washing power is weak, but with a high disinfecting strength. It is particularly effective for Gram positive and Gram negative bacteria. These are not irritating to the biological body, with no metallic corroding properties, therefore are applied to the finger tips and apparatus as disinfection agents. Benzalkonium chloride or benzethonium chloride is applied as 0.05 to 0.1 % disinfectant solution to the finger tips and skin, or as 0.01 to 0.025% disinfectant solution to the wounds.

G. Organic dyes

There are acrinol and methylrosanilinium chloride. Acrinol displays efficacy for streptococci, and staphylococci but are inactive against spores and virus. This is applied as a 0.02 to 0.2 % solution for the disinfection of the skin and mucosa of the wounded region or festering wounds. The latter agent displays bacteriocidal activity against Gram positive bacteria with 0.1 to 0.2 % solution.

IX. Emergency medicines

Among the patients undergoing implant treatment, there are elderly or have concomitant systemic diseases. During the invasive implant surgery, these patients are predisposed with the unforeseen circumstances therefore are required to act promptly with a suitable solution to the problem. In other words, in the case of an emergency treatment, an accurate diagnosis, and timely treatment are necessary.

The administrations of the pharmaceutical agents below should also be considered. As these drugs are mostly administered via the intravenous route, practices of securing a vein are desired.

A. Atropine sulphate

It is a parasympathetic neuroleptic agent, and show efficacy for bradycardia and decreased blood pressure. The common abnormal condition arising in dental treatments including implant surgery is the neurogenic shock. This is thought to be due to the tensing of the parasympathetic nerves, therefore the administration of this agent is apt for the prevention of this condition. 0.5 mg of this is administered, intravenously, and increased as required.

B. Adrenaline

This is a classic sympathomimetic agent that show higher efficacy for the substantial decrease in blood pressure, or anaphylactic shock. The 1mg/ml ampule is diluted ten times, then 0.1 mg (i.e. 1 ml) is gradually administered intravenously. The hypodermic injection of 0.3 mg is effective against anaphylactic shock. A pre-filled syringe that can readily be used for anaphylactic shock can be purchased.

C. Tranquilizers

Diazepam or midazolam are infused, intravenously as a psycho-sedation for cases of hyperventilation syndrome. The benzodiazepams also show effectiveness for convulsion which is a toxicity symptom from local anesthetics. The overdose can lead to respiratory suppression and arrest therefore care must be taken when administering.

D. Calcium channel blocker

As antihypertensive drugs, Nicardipine hydrochloride and nifedipine, which are effective for emergency procedures, are adopted for the abrupt rise in blood pressure during the treatment. Principally, it is administered via intravenous route, but orally formulated nifedipine for internal use can be administered via the sublingual route. The overdose can cause abrupt decrease in blood pressure overdose, therefore care must be taken at the time of administration.

E. Nitrous acid

Used as a coronary vasodilator. It can be applied by the intravenous infusion for the acute exacerbation of ischemic heart disease, or by appending a patch containing active ingredients to the chest.

X. Others

A. Propofol

It is applied widely as an intravenous anesthesic agent, it is also used in implant surgery as an intravenous sedation methods. Amongst the intravenous sedatives, it has the advantage of being simple to manipulate the doses due to its fast induction, and prompt awakening. It is often induced via infusion pumps or syringe pumps. The introducing dose is 0.3 to 1 mg/kg which is rapidly administered, and then the maintenance dose for sedation is infused at the rate of 2 to 3 mg/kg/h. A rapid administration can cause vascular pain (angialgia). Due to the drug property, the overdose can lead to respiratory

suppression or arrest, and decreased blood pressure, particularly in the elderly, therefore monitoring the patient's respiration and circulation is essential if used. In addition, oxygen pumps should be prepared for prompt inhalation.

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