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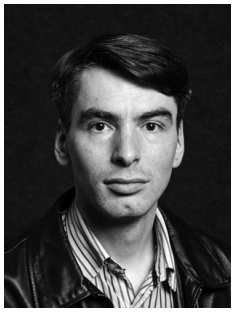
Drug interactions in anaesthesia practice: a basic review for residents



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Summary

This article presents fundamental aspects of drug interactions (chemical, pharmacodynamic, pharmacokinetic), including definitions for additive, synergic and antagonistic effects. Graphical modalities of drug interactions are also reproduced, including izobolograms and tridimensional surface models (Minto models). We also review the effects of the main drug interactions between hypnotics and opioids, between halogenated agents and opioids, between opioids and myorelaxants, between various post-operative analgesics and between other groups of drug. *Anestezjologia i Ratownictwo 2010; 4: 99-109.*

Keywords: interactions, pharmacokinetic, pharmacodynamic, isobologram, effect

Drug interactions: fundamental aspects

- **Introduction**

Combinations of drugs have been used since immemorial times, to cure illness and reduce suffering. The concomitant use of multiple drugs can target several therapeutic goals or can focus a common action upon one single goal or disease. The positive effects of drug interactions are always sought, for example:

- Reducing the necessary dosage of the drug while producing the same effect and decreasing its toxicity and the incidence and magnitude of side effects;
- Minimising or slowing down the development of resistance to the drug;
- Producing a selective and synergic effect on the target.

Studying and modelling drug interactions with a goal to identify the optimal interactions represents one of the priority fields of modern pharmacology. In the current medical climate, the anaesthetist is likely a specialist in perioperative medicine. This among other missions includes the necessity of being acquainted not only with the drugs prescribed in the operating room, but also during the whole perioperative period, including the dosages, routes of administration, and the special features of metabolism, elimination and possible interactions.

It is estimated that the incidence of drug interactions producing significant undesirable clinical manifestations, is 3-5% of patients taking a few drugs simultaneously, and up to 20% of patients taking 10-20 different drugs. Because the majority of hospitalized patients receive 6 drugs on average, the importance of the problem is evident [1,2].

There are several types of drug interactions, including pharmaceutical, pharmacokinetic and pharmacodynamic.

- **Pharmaceutical interactions (chemical)**

Pharmaceutical interactions are basically chemical nature. For example, the alkaline solution of thiopental, mixed with an acid solution of succinylcholine, precipitates when the two are mixed in the same syringe.

- **Pharmacokinetic interactions**

Interactions that occur at the stage of absorption,

distribution, metabolism and excretion are of the pharmacokinetic type. For example, cholestyramine prevents absorption of thyroxine, cardiac glycosides, corticosteroids and warfarin. Antibiotics can modify the intestinal flora and then the synthesis of vitamin K decreases, thus intensifying the effect of oral anticoagulants [3].

Drug interactions can also manifest themselves at the stage of metabolism. The induction or inhibition of cytochrome P450 system activity has the largest impact on drugs administered orally, as they mandatorily pass the hepatic barrier after absorbtion.

Examples of drugs that are influenced by the P450 inductors include: oral anticoagulants, quinidine, oral contraceptives, corticosteroids, theophylline, mexiletine, some beta-blockers, and anti-HIV/AIDS medication. P-glycoprotein transport systems are almost always omitted from the presentation of drug interactions, in spite of their major role in transportation and distribution of many drugs. P-glycoprotein is an ATP-dependent transporter (a molecular pump), which ejects various molecules (substrates) from the cell cytoplasm, forming a special protection created by nature. The first line of P-glycoproteic transporters is located at the apical (luminal) end of the enterocyte. When a substrate enters the cell according to the concentration gradient P-glycoprotein ejects it back into the intestinal lumen against the concentration gradient, which is an energy dependent consuming ATP process. P-glycoprotein also covers the blood-brain barrier (BBB), thus protecting the neuronal microenvironment from the penetration of xenobiotics. P-glycoprotein is located on the endotheliocyte membrane lining the capillary lumen. Drugs which are ejected from BBB into the capillary lumen by the P-glycoprotein system are numerous: carbamazepine, corticosteroids, cyclosporine, dexametasone, digoxin, morphine, ondansetron, phenytoin, tacrolimus, risperidone, tricyclic antidepressants etc.

Many drugs inhibit the activity of P-glycoprotein transporters, thus significantly increasing the absorption of certain drugs from the intestinal lumen into the blood. Similarly, a substance which has penetrated into the blood from the intestine or is administered intravenously will pass the BBB and accumulate in the neuronal microenvironment. In such circumstances, drug toxicity can manifest itself. Potent inhibitors of P-glycoprotein include: lidocaine, fluoxetine, atorvastatine, erythromycine, clarithromycine, itraconazole, quinidine, cyclosporine A, lovastatine, midazolam, omeprazole, propranolol, simvastatine, and verapamil.

Relatively few drugs are P-glycoprotein inducers. A hyperactive P-glycoprotein could lead to a loss of drug efficacy. Known inducers of P-glycoprotein include aspirin, rifampicin, and trazodone. For example, the administration of rifampicin and digoxin at the same time will decrease the serum concentration of the glycoside mainly through this mechanism. The number of drugs found to interfere with P-glycoprotein activity is increasing exponentially and it is important to know these interactions, especially when administering drugs with a low therapeutic index, such as digoxin or tacrolimus (immunosuppressant).

Many drugs are bound largely by albumin (acidic drugs) or by alpha-glycoprotein (alkaline drugs), and only the free fraction of the drug exerts a pharmacologic action. The dislocation of a drug from the protein binding sites increases its free fraction, and so its clinical (therapeutic and toxic) effects.

- **Pharmacodynamic interactions**

These occur as a result of several mechanisms that are still mostly not well-understood. At the cellular level, a drug may increase the affinity of another drug for its receptor, or on the contrary, can decrease it. A drug may also interfere with the translation mechanism of the intracellular signal produced by a different drug (e.g. enhancing the arrythmogenic effect of beta-adrenergic agonists by volatile anaesthetics by increasing both the adenylatcyclase activity or by increasing MAC' in alcoholics, due to tolerance phenomenon development of the GABA-ergic receptor). Another mechanism is the effect exerted on the neuromediator uptake, release of which is modified by a different drug (e.g. antagonization of neuromuscular block by anticholinesterases) [4]. A pharmacodynamic interaction can also occur by influencing different mediator systems, the final effect of which, however, is common at the cellular and subcellular levels.

- **Notions of synergism, amplification, or potentiation**

There are 7 different definitions of synergism and 13 different methods of its quantification. This has become the source of many controversies and confusion concerning the assessment of the effects of drug combinations [5]. Let us consider a very simple equation: Drug A is combined with Drug B. If Drug A produces a certain

effect and Drug B does not produce any effect, but in combination the final effect is greater than that of the Drug A alone, the phenomenon is called ***potentiation*** or ***amplification.*** The effect is described simply as "effect amplified by a certain percentage" or "effect amplified by a number of times".

If each of the Drugs A or B produce a certain effect, then in combination they can exert a **synergistic**, ***additive*** or ***antagonistic*** effect. According to the definition, synergism is an effect greater than the additive effect, and antagonism – an effect lower than additive. Therefore it is crucially important to properly define what an additive effect is, because definitions of synergism or antagonism are stemming from here. In the majority of cases, researchers or clinicians combine drugs to achieve a synergistic effect. However, common mistakes of analysis and interpretation occur:

1. A + B > A or A + B > B does not say anything about synergism. It is a simple mathematical statement, not requiring any evidence nor a statistical analysis, e.g. the calculation of the *p* value.
2. The additive effect is not a simple mathematical sum of the effects of the two or more drugs. If A and B each inhibit some process by 30%, then the additive effect isn't 60%, because if A and B would inhibit each other by 60% the sum effect cannot be 120%.
3. If A or B each inhibit some process by 60%, we can confirm in a very simplistic way that in combination, the additive effect is 84% of the inhibition (based on Webb's reasoning (1963)). Such problems can be solved in the following manner: (1-0.6)(1-0.6) = 0.16; 1-0.16 = 0.84). However, this method does not take into account the slope of the dose-effect curve (e.g. hyperbolic or sigmoid) [6].

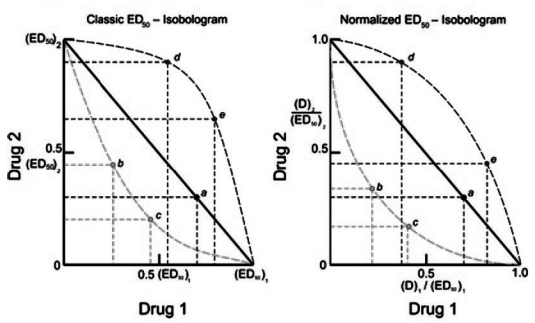


Figure 1. Expression of pharmacodynamic drug interactions via the classical and normalised isobologram

One of the methods of presenting the drug interaction type is the classical isobologram and the classical normalized isobologram (Figure 1) [6].

In the classical isobologram, the ***x*** axis corresponds to the 1st drug, and the ***y*** axis – to the 2nd drug. The drug dose in the classical isobologram is expressed in usual quantitative units (mg, AU, IU etc.), meanwhile in the classical normalized version – as a fraction of the actual dose to the dose that produces 50% of the maximal effect (ED_{50}). In both cases, the ED_{50} dose can be extended to an ED_x dose, which produces ***x***% of the effect.

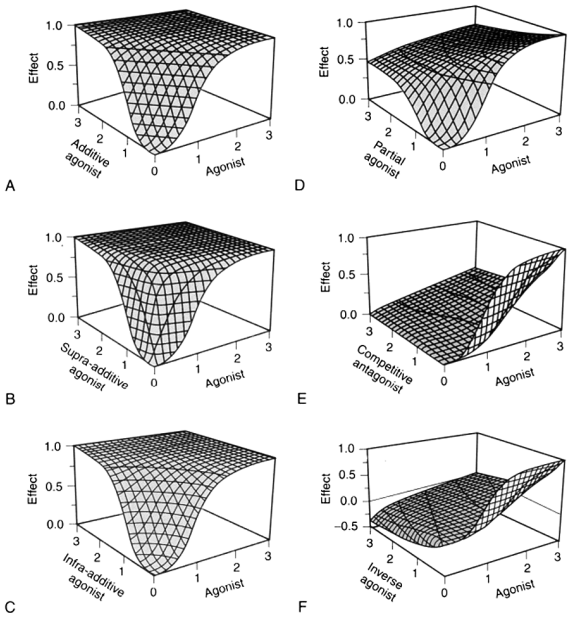
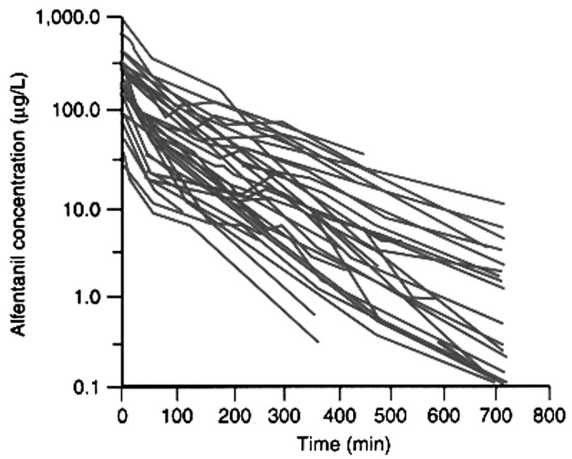


Figure 2. The expression of pharmacodynamic drug interactions by the means of the Minto model.

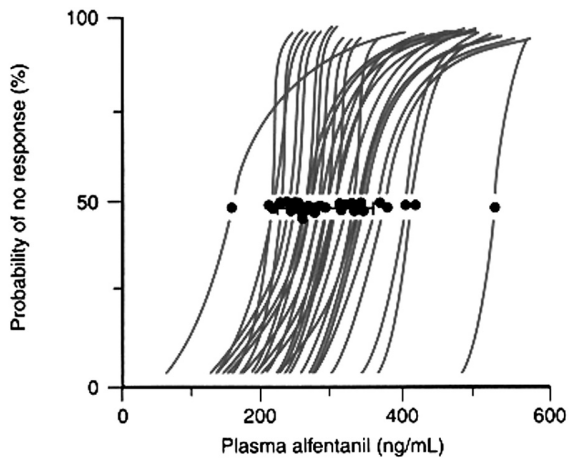
Legend: ***A*** *– additive type interaction between two agonists that have the same mechanism of action (eg. fentanyl and alfentanil).* ***B*** *– supra-additive (synergistic) interaction between two agonists (eg. isoflurane and fentanyl).* ***C*** *– infra-additive (antagonistic) interactions between two agonists (eg. cyclopropane and N_2O or tramadol and morphine).* ***D*** *– interaction between a complete and a partial agonist (eg. fentanyl and nalbuphine).* ***E*** *– interaction between a complete antagonist and a complete agonist (eg. naloxone and fentanyl).* ***F*** *– interaction between a inverse agonist and a complete agonist (eg. experimental substance R019-4063 and midazolam)* [7].

The isobolographic method does not account for the dose ratio, the slope of the dose-response curves, the

mechanism of action or the measuring units of the drug quantity. When combining the drugs, if the magnitude of the quantified effect is situated on the hypotenuse (point ***a***), the effect is ***additive***. If the points fall in the lower left side of the isobologram (e.g. points ***b, c***), then the drug interaction is synergistic, but if the points fall in the right upper side (e.g. ***d, e***), the sum effect is antagonistic (infra-additive). The classical isobologram can be easily built in the case of administering drugs in constant doses. If an examined drug is administered in variable doses and the other drug is administered in fixed doses, quantification of the interaction type can be made with the help of the classical normalized isobologram.



a



b

Figure 3. An example of pharmacokinetic (A) and pharmacodynamic (B) variability of alfentanil [9].

Another, more sophisticated method of presentation of pharmacodynamic interactions, which also takes into consideration the co-report between the doses of the studied drugs, is the tridimensional surface model (Minto model). Figure 2 shows the Minto surfaces typical of the existent pharmacodynamic interactions between anaesthetics [7].

Pharmacokinetics and pharmacodynamics are variable in the population [8,9]. Resultant drug interactions therefore have an individual profile. Figure 3 presents the pharmacokinetic and pharmacodynamic variability of alfentanil.

On the right side (A) of Figure 3 are presented the dynamics of the decrease in the plasma concentration of alfentanil in 45 patients, administered 50 µg/kg of alfentanil. The left side (B) of Figure 3 presents the dose-response curve of alfentanil in abdominal surgery in 34 patients. The black circles indicate the Cp_{50} for each patient.

Drug interactions: clinical aspects

- **Interactions between hypnotics and opioids**

The absolute majority of interactions between intravenous anaesthetics are synergistic, some are additive, others are even infra-additive (antagonistic). However, the magnitude of interactions is not identical for the same class of drugs or in different stages of anaesthesia (e.g. at the moment of loss of consciousness or at the moment of skin incision) [10].

The bispectral index (BIS) was suggested as a reference parameter, which reflects the action of hypnotics on the brain. In the presence of fentanyl, alfentanil, sufentanil or remifentanil, the loss of consciousness occurs at much lower plasma concentrations of propofol and at greater BIS values, in comparison with the administration of propofol alone. These results have lead to the hypothesis that the hypnotic effect of propofol is potentiated by the analgesic doses of opioids (fentanyl, sufentanil, alfentanil), but without modifying the BIS values. On the other hand, maintaining the target plasma concentrations of 0.5, 2.5 and 10 mg/ml of remifentanil via the intravenous perfusion, combined with a propofol perfusion, adjusted to maintain BIS values at a level of 60, leads to a dose-dependent decrease of BIS, which highlights the sedative effect of remifentanil.

Both thiopental and propofol can be combined safely with opioids, but both hypnotics potentiate the

hypotensive effect, caused by venous dilatation and the diminution of the ventricular filling pressure, sympathetic outflow and myocardial contractility. Administration of a combination of propofol and an opioid causes loss of consciousness and blocks the reaction to nociceptive stimulation, while none of the drugs achieve both of the effects to a sufficient degree when administered alone [11].

Propofol-fentanyl or profol-sufentanil anaesthesia can reduce mean arterial pressure to a level which can compromise coronary perfusion, especially during induction. In healthy volunteers, the addition of alfentanil (C_{es} of 50 or 100 ng/ml) did not influence the BIS value induced by propofol, but blocks the elevation of BIS during nociceptive stimulation.

Administration of fentanyl until reaching plasma concentrations (Cp) from 1.5 to 4.5 mg/ml, reduces the need in propofol for maintaining stable arterial pressure, but delays the moment of awakening, opening of the eyes and special orientation [12]. Morphine produces a stronger synergistic effect with hypnotics than piperidine opioids (fentanyl). Fentanyl and alfentanil plasma concentration increases with concomitant propofol administration.

Benzodiazepines potentiate the effects opioids and reduce the dose required for producing loss of consciousness, often by synergistic interaction. On the contrary, the combination has an infra-additive effect for analgesia. Midazolam amplifies the analgesic effect of fentanyl. The benzodiazepine-opioid combination is however synergistic for many other effects, leading to a decrease of arterial pressure, systemic vascular resistance, heart rate, cardiac output and the threshold for respiratory depression.

The interaction between benzodiazepines and many other hypnotics is highly synergistic.

Other induction agents, such as etomidate or ketamine, can be combined in low doses with opioids without causing cardiovascular instability. Thus, induction with etomidate (0.25 mg/kg) and fentanyl (6 μg/kg) causes less arterial hypotension than induction with propofol (1mg/kg) and fentanyl (6 μg/kg). Establishing drug dosage and administration regimens for obtaining optimal plasmatic concentrations (Cp) to maintain hemodynamic stability during surgery, especially under conditions of a wide range in intensity noxious stimuli, could be useful practically.

Interactions between three drugs also have been studied. It seems that the administration of a third drug does not further increase the level of synergy of the interaction [10]. Some clinicians administer low doses of midazolam (ex: 30 μg/kg) before induction with propofol, with the hope that the association has an additional synergistic effect in combination with opioids (in clinical sense – lower doses for induction and faster onset of action. However this "co-induction" technique has questionable efficacy.

- **Interactions between halogenated anaesthetics and opioids**

Inhalational anaesthetics are frequently combined in low doses (1/3 – 1/2 MAC) with opioids for obtaining amnesia, immobility and intraoperative haemodynamic stability. These combinations are well tolerated by patients with altered cardiac function. Studies conducted on the combinations of opioids and modern halogenated agents (sevoflurane, desflurane, isoflurane) have demonstrated cardiac output stability and an insignificant decrease in mean arterial pressure. However, myocardial ischemia cannot always be improved with use of this combination, despite apparently good haemodynamic control. Halotane increases the sympathetic outflow and the risk of myocardial ischemia in patients with altered cardiac activity respectively. Early administration of a low dose of fentanyl (1,5 μg/kg) or alfentanil (10 μg/kg) significantly reduces this undesired effect.

Nitrous oxide administered alone maintains a stable haemodynamic condition. In association with opioids, nitrous oxide does not induce wall motion abnormalities or ST segment deviations in patients with myocardial ischemia. N_2O produces analgesia through the release of a peptide precursor of proenkephalin, an endogenous opioid.

This fact suggests that the interaction between opioids and nitrous oxide is neither additive nor synergistic, and the use of this drug combination under balanced anaesthesia does not seem reasonable. Probably, the amnesic effect or the intraoperative conditions can be somehow improved by N_2O, but it does not produce any other effect that could not have already been produced by the association of an opioid with a benzodiazepine or a hypnotic [13].

Fentanyl reduces the MAC of isoflurane by approximately 80% at skin incision. A non-linear relation between the Cp of fentanyl and the reduction of MAC of isoflurane (Figure 4) has been demonstrated [14]. Benzodiazepines reduce the MAC of halogenated

agents by approximately 30%. Comparing the potency of the opioids through the prism of reduction of the MAC of inhalational analgesics, we see the relation – fentanyl:sufentanil:alfentanil:remifentanil = 1:12:0.06:1.2.

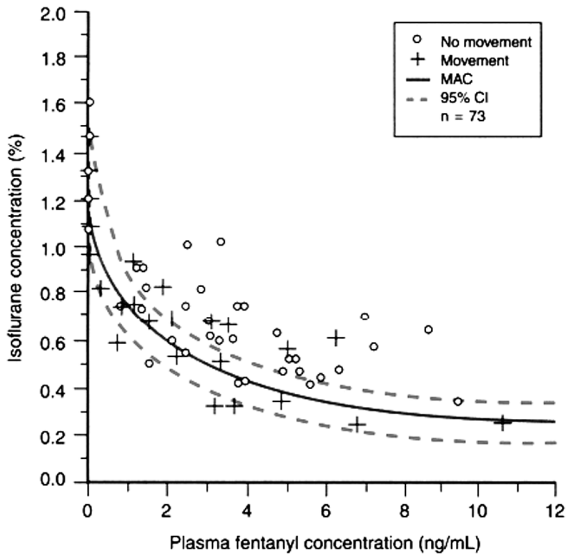


Figure 4. Decreasing the MAC of isoflurane by increasing of the Cp of fentanyl

- **Interactions between opioid analgesics and muscle relaxants**

Pancuronium was used frequently since the dawns of anaesthesia with mega-doses of opioids (*stress-free anaesthesia*). It was reported that the vagolytic action of pancuronium could mitigate the opioid-induced bradycardia and maintain stable blood pressure. However, the interaction between pancuronium and opioids can be modified by many factors, such as the dosage, frequency and the route of administration of the drug, premedication, volemic repletion, cardiac contractility and the use of other drugs and their effect upon the autonomic nervous system [15].

Combining vecuronium with large doses of opioids produces negative chronotropic and inotropic effects, with bradycardia, decreased cardiac output, hypotension and the need for vasopressor support. In comparison with vecuronium (0.15 mg/kg), the pancuronium (0.15 mg/kg) in patients undergoing coronary arterial bypass causes tachycardia more frequently (32% *vs* 7%), but without increasing the incidence of perioperative myocardial ischemia [16].

Metocurine (0,5 mg/kg) causes less haemodynamic fluctuations than pancuronium [17]. Doxacurium does not produce measurable haemodynamic effects in cases of sufentanil-midazolam anaesthesia. Pipecuronium, in doses up to $3ED_{95}$, does not exert any effects on haemodynamics in cases of sufentanil-midazolam anaesthesia. Mivacurium causes a slight decrease in arterial pressure, probably due to histamine release if rapidly (<30 sec) administered in doses greater than $2ED_{95}$ [18].

- **Interactions between analgesics used in the postoperative period**

The simultaneous administration of different classes of analgesics is more and more common and has a goal to optimize the quality of postoperative analgesia and maximally limit the probability of side effects at the same time. Pharmacokinetic and pharmacodynamic interactions in the case of combined therapy can be favourable and unfavourable. The utility of associations of analgesics has not been investigated for the majority of therapeutic schemes used perioperatively on a daily basis.

Table 1 reviews the mechanism of action of the main analgesics.

- **Various drug interactions in anaesthesia and intensive care practice**

Monoamineoxidase inhibitors (MAOIs) cause the most severe interactions with opioid analgesics, potentially even fatal. These effects are well known in the case of meperidine. Interactions between opioids and MAOIs are both excitatory and inhibitory. The excitatory type of interaction causes serotonin syndrome, which is manifested by agitation, headache, haemodynamic instability, fever, muscle rigidity, convulsions and coma. Meperidine, but not morphine, blocks serotonin reuptake in neuronal synapses. Inhibitory interactions are manifested by respiratory depression, hypotension and coma. These toxic effects are caused by inhibition of hepatic microsomal enzymes, followed by accumulation of meperidine in the organism [36].

Opioid analgesics can inhibit the voltage-gated Ca^{++} channels via the G protein. Studies on animals have shown that L-type Ca^{++} channel blockade potentiates opioid mediated analgesia. Systemic administration of nifedipine potentiates the analgesic effect of opioids in animals and humans. Intrathecal administration of diltiazem, verapamil or nicardipine

Table 1. The mechanism of action of the main analgesics used perioperatively

Drugs	Mechanism of action
Paracetamol	Not well understood. Central action.
NSAIDs	COX-1 and/or COX-2 inhibition. A central action presupposed.
Opioids	Specific (miu, kappa, delta) receptors of the brain, medulla, and periphery (absent in constitutive states and expressed at the sites of incipient inflammation).
Nefopam	Central monoaminergic and less opioid action.
Tramadol	Central opioid action, increases the inhibitory tonus of the efferent serotonergic and noradrenergic pathways at the spinal and supraspinal levels.
Ketamine	NMDA receptor antagonist.
Local anaesthetics	Blockage of the nervous conduction through the inhibition of the sodium channels.
Clonidine	Central alfa-2 receptor agonist. May be of interest for intra-articular administration.
Gabapentin	Inhibition of voltage-gated calcium channels.

Table 2. Interactions between non-opioid analgesics in the postoperative period

Drugs	Comments
Paracetamol - Nefopam	No bibliographical references were found about this combination.
Paracetamol - NSAIDs	Combination often prescribed in the postoperative period. The association allows a better analgesia than the one obtained by using paracetamol alone, but not greater than in the case of using NSAIDs as monotherapy. Paracetamol does not bring any additional benefit when prescribed in combination in the case of moderate pain [19,20].
Paracetamol - Tramadol	Studied insufficiently. The superiority of this combination, versus each of the drugs used alone has been reported [21].
NSAIDs - Nefopam	A very synergistic combination. At the end, ED_{50} reaches up to 1,75 mg (0,9-2,3 mg) for nefopam and 4,3 mg (2,2-6,5 mg) – for ketoprofen [22].
NSAIDs - Tramadol	An additive association, with no significant interest for clinical practice [23].

enhances opioid-mediated analgesia [37,38].

Erythromycin reduces cytochrome P450 oxidative activity. Alfentanil, but not sufentanil, may have a prolonged action in patients treated with erythromycin. Erythromycin gives a 2-3 fold increase in the effects and duration of action of midazolam. A 7-day treatment with erythromycin will increase the duration of respiratory depression and the degree of sedation in cases of administering alfentanil but not sufentanil [39].

Cimetidine may also increase the duration of action of opioid analgesics and benzodiazepines by decreasing hepatic blood flow and reducing enzymatic activity. Other drugs that inhibit liver enzyme activity may prevent the conversion of codeine to morphine, leading to inadequate analgesia [40].

Esmolol, the short acting beta-1-blocker, significantly reduces the MAC for izoflurane in the presence of alfentanil and has practically no effect on the MAC in the absence of an opioid. The mechanism of this interaction remains unknown [41].

Magnesium has antinociceptive effects by antagonizing the NMDA receptor. Premedication with $MgSO_4$ (50 mg/kg), then continued with intraoperative perfusion in doses of 8 mg/kg/hour significantly reduces the post-operative need in opioids. However, magnesium barely passes the blood-brain barrier, and may cause arterial hypotension, muscle weakness and sedation [42].

Heparin decreases the plasma protein binding of diazepam. Consequently, the Cp of free diazepam increases by 200% after administration of 1,000 units of heparin [43].

Ethanol, barbiturates and other central nervous system depressants potentiate the sedative effects of benzodiazepines. Ethanol, opioids, antihistamines will increase the depressant effect of barbiturates. Chronic alcohol abuse, despite the ingrained beliefs, does not increase the thiopental requirements for achieving induction in anaesthesia [44].

Ketamine potentiates the effect of non-depolarizing muscle relaxants. Combining ketamine with theophylline decreases the threshold for convulsions.

Table 3. Interactions between morphine and non-opioid analgesics

Drugs	Comments
Paracetamol	When comparing monotherapy morphine or paracetamol with combined therapy, their association produces a decrease of about 20% of the necessary dose of morphine in the postoperative period, but not a reduction of the pain scores or side effects [24,25].
NSAIDs	The association allows the reduction of the postoperative consumption of morphine by about 50% and a reduction in pain scores, in comparison with monotherapy with morphine or NSAIDs. The decrease in frequency and intensity of side effects (nausea, vomiting, postoperative ileus, drowsiness) is proportional to the dose of morphine reduced [26].
Nefopam	Controversial results. Some studies report about a 30% reduction of the necessary postoperative dose of morphine, when others demonstrate an infra-additive effect. In any case, the incidence and intensity of side effects is not affected. The combination seems to be interesting in perspective, because the induction of an antihyperalgesic effect is assumed [27].
Tramadol	Combined with morphine, tramadol causes an infra-additive effect, so it is not recommended. The ED_{80} analgesic dose for tramadol is 260 mg, which by far exceeds the usual dose of 100 mg prescribed overnight. In conclusion, tramadol is not a drug of choice for postoperative analgesia [28,29].
Ketamine	The combination prevents the development or reduces the intensity of postoperative hyperalgesia and delays the effect of acute tolerance in the case of administration of morphine in continuous infusion. The overnight morphine consumption is reduced by about 30%, however without a reduction in the frequency or intensity of side effects [30,31].
Local anaesthetics	Contradictory results, without a reduction in the pain scores or side effects of morphine in the postoperative period. Bowel function recovery is accelerated in the case of intravenous administration of lidocaine [32].
Clonidine	Allows a decrease in morphine consumption by 20-30% and a parallel proportional reduction of side effects of morphine [33,34].
Gabapentin	In combination with morphine it significantly reduces postoperative pain scores, morphine requirements and the frequency and intensity of side effects. The optimal dosage of gabapentin for this indication is not yet established [35].

Diazepam reduces the cardiostimulatory effects of ketamine and increases its half-life. Propranolol, phenoxybenzamine or other simpaticolytic drugs unmask the cardiodepressant effects of ketamine. Ketamine causes cardiac depression when administered in patients anesthetized with halothane (this is also true for other halogenated anaesthetics, but to a lesser extent). Ketamine administration reduces opioid-induced hyperalgesia and tolerance phenomenon, with beneficial effects on the quality of postoperative analgesia. It was demonstrated that the administration of ketamine in doses of 2.5 or 10 mg intravenously and of alfentanil in doses of 0.25 to 1 mg intravenously, does not make any difference to the final analgesic effect. Combining ketamine with morphine (mg per mg) reduces the daily need in the opioid analgesics postoperatively [45].

Gabapentin, a GABA structural analogue, is the drug of choice for treating neuropathic pain. Administered pre-operatively in a dose of 900-1200 mg orally, it significantly reduces post-operative morphine requirements, increases the quality of analgesia and significantly decreases the likelihood of the development of persistent post-operative pain [46].

Droperidol antagonizes the effects of levodopa and may precipitate parkinsonian symptoms. Renal effects of dopamine are counteracted by droperidol. Theoretically, droperidol may antagonize central alpha-adrenergic effects of clonidine and precipitate rebound hypertension. Droperidol attenuates the cardiovascular effects of ketamine [47].

Because of the exceedingly high value of the MAC, N_2O can not be used as an anaesthetic alone, but only in combination with other volatile or intravenous anaesthetics. A gas mixture that contains 65% N_2O reduces the MAC of volatile anaesthetics by 50%. Although it is not the best carrier gas, it attenuates the circulatory and respiratory effects of halogenated anaesthetics. In addition to the effect of the second gas caused by N_2O, the flow of the nitrous oxide through the vaporiser influences the concentration of the halogenated agent delivery. For example, if the N_2O flow is decreased (respectively increasing the airflow or O_2-flow in the gas mixture), this increases the delivery of the halogenated agent as well, despite the maintenance of the same vaporiser settings. This disparity is explained by

the different solubility of nitrous oxide and oxygen in the liquid halogenated anaesthetic [48,49].

Myocardial depression produced by halothane is enhanced by beta-blockers (e.g. propranolol) and calcium channel blockers (e.g. verapamil). Although halothane combined with tricyclic antidepressants and monoamine oxidase inhibitors results in intra-operative arterial pressure fluctuations and arrhythmias, but the both are not absolute contraindicated. The combination of halothane with aminophylline causes serious ventricular arrhythmias [50].

Adrenaline can be used safely on a halothane background, up to summary quantities of 4.5 μg/kg. Desflurane, sevoflurane and izoflurane do not sensitize the heart to the arrhythmogenic effect of catecholamines [51,52].

Although awakening from anaesthesia is more rapid in the case of desflurane, in comparison with izoflurane, the transition from izoflurane to desflurane just before the end of anaesthesia does not accelerate the awakening process, or the time of the patient's discharge from post-anaesthesia care unit. Desflurane can produce delirium during the awakening process in some paediatric patients [53].

Local anaesthetics potentiate the neuromuscular blockade produced by non-depolarising muscle relaxants. Succinylcholine and ester-type local anaesthetics are metabolised by pseudocholinesterases; their concomitant administration might potentiate the effects of both drugs. Cimetidine and propranolol reduce hepatic blood flow and the clearance of lidocaine. This increases its plasmatic concentration and it is potential systemic toxicity consequently. Opioids and alpha-2-agonists potentiate the analgesic effect of local anaesthetics [54,55].

Concomitant administration of steroids, muscle relaxants and aminoglycosides should be avoided to reduce the risk of 'ICU Myopathy' (ICUM). ICUM is a term used to describe the generalized muscle dysfunction that appears in critical patients, which is manifested by flaccid muscle weakness of the limbs, neck, face and diaphragm. Ophthalmoplegia and osteotendinous hyporeflexia are often found. There are over 50 drugs that affect neuromuscular transmission, but muscle relaxants, aminoglycosides, clindamycin and colistin particularly cause pharmacological muscle denervation. As a result, the number and sensitivity of the cytoplasmic receptors to glucocorticoids increases. Therefore, the initiation of a vicious circle, when steroids, aminoglycosides and muscle relaxants are administered concomitantly is possible [56].

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Piśmiennictwo

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