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Undesirable drug interaction in palliative medicine

Abstract

The importance of drug interactions in palliative care is acquiring more and more practical importance. In the polytherapy used in palliative care, drugs can induce a number of interactions and increase the risk of unwanted drug reactions.

This paper discusses the importance of drug-drug interactions in clinical practice.

Key words: palliative care, pharmacotherapy, drug interactions

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Introduction

The importance of the interaction of the drugs used in palliative medicine is acquiring more and more practical importance. The patient with advanced disease often obtains a few drugs at the same time, which may enter into unfavourable interactions, both pharmacokinetic and pharmacodynamic, resulting in undesirable consequences. Another practical problem is the fact that drugs administered simultaneously may have a shared profile of undesirable effects with the capacity to increase.

The general condition of the patient with advanced disease repeatedly undergoes dynamic changes, which cause new symptoms to appear. Thus, distinguishing which of the symptoms is the result of the progression of the disease and which may result directly from the undesirable effects of the drugs used is an important element in evaluating the patient's status.

Palliative patients were once frequently treated with chemo- and hormone therapy, which may im-

pair organ functions crucial for the pharmacokinetics of drugs. The occurrence of undesirable post-drug effects is an additional risk factor. Hypoalbuminaemia is observed in the majority of patients, which is important in drugs with a close affinity to albumins. In such situations, a free drug fraction increase is observed in the drugs, which increases the risk of undesirable effects.

Interaction with drugs used in palliative pain therapy

Interactions with non-steroidal anti-inflammatory drugs (NSAIDs)

Non-steroidal anti-inflammatory drugs are one of the most frequently used type of drug in palliative medicine. With regard to how they suppress prostaglandin synthesis, they may enter into unfavourable pharmacodynamic interaction with drugs used in the pharmacotherapy of cardiovascular system diseases (angiotensin-converting enzyme inhibitors, AT1 receptor antagonists, beta-adrenolytics,

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especially carvedilol and nebivolol), loop diuretics, and the result of this interaction is to limit the effectiveness of circulatory drugs and diuretics [1]. It is worth mentioning that patients with impaired renal function who take NSAIDs and loop diuretics simultaneously have an increased risk of nephrotoxicity.

It is important for the risk of interaction that the majority of NSAIDs bind with blood proteins to a high degree (over 90%). Consequently, special care should be taken when simultaneously using other drugs (sulphonylurea derivatives, oral anticoagulants, or anti-epileptics) which bear a NSAID-like affinity for albumins. The clinical effect of these interactions is an increase in the free fraction of drugs displaced by NSAIDs and the occurrence of undesirable effects.

A frequent mistake observed in clinical practice is the simultaneous administration of two or even more NSAIDs. It should be remembered that this does not lead to the synergism of an analgesic effect but significantly increases the risk of gastrointestinal toxicity, and liver and kidney damage. One of the major undesirable effects of NSAIDs is drug-induced gastropathy. This risk increases when the patient simultaneously takes other drugs which may damage the upper part of the digestive tract, in particular:

- glucocorticosteroids;
- oral bisphosphonates;
- oral anticoagulants;
- drugs from the group of serotonin reuptake inhibitors, which not only inhibit the reuptake of serotonin in the structures of the central nervous system but also suppress this uptake to platelets;
- spironolactone, which inhibits fibrosis processes that accompany the healing of digestive tract damage and are induced by NSAIDs.

Moreover, the combination of NSAIDs with spironolactone may cause hyperkalaemia.

The use of drugs from the H2 receptor antagonist group while NSAIDs are administered is a mistake. H2 blockers do not protect the digestive tract from being damaged by NSAIDs but mask the symptoms of this damage [2].

In a clinical situation, when the administration of gastric acid secretion inhibiting drugs together with NSAIDs is necessary, proton pump inhibitors are the best choice.

Care in the use of NSAIDs should be taken in patients with liver damage because these drugs may induce oxidative stress in hepatocytes, cause damage to the mitochondria and apoptosis of hepato-

Table 1. Drugs suppressing CYP2C9 activity

Drugs
Fluoxetine
Fluvoxamine
Paroxetine
Sertraline
Amiodarone
Anastrozole
Cimetidine
Ranitidine
Clopidogrel
Fluconazole

Table 2. Drugs inducing CYP2C9 activity

Drugs
Cyclofosfamide
Ifosfamide
Valproic acid

cytes. Diclofenac may directly damage hepatocytes, which should be considered if the patient requires other potentially hepatotoxic drugs.

With patients aged 65 and older, NSAIDs should be very cautiously coadministered with angiotensin-converting enzyme inhibitors and loop diuretics because this combination in such patients leads to renal function impairment. Caution should be used during the co-administration of NSAIDs with anti-platelet drugs, owing to the increased risk of blood loss.

Some NSAIDs (diclofenac, ibuprofen, naproxen, piroxicam) are actively metabolized by the CYP2C9 isoenzyme: their use introduces an increased risk of pharmacokinetic interaction with other drugs which inhibit or activate this isoenzyme.

The most frequently used drugs in clinical practice which induce the activity of the CYP2C9 isoenzyme are presented in Table 1 [3]. Drugs that suppress its activity, and thus extend the half-life of the above-mentioned NSAIDs, are presented in Table 2.

Interactions with metamizole

Metamizole should be cautiously co-administered with neuroleptics and phenothiazine derivatives due to the risk of severe hyperthermia.

Metamizole increases the concentration of methotrexate in blood serum, increasing its toxicity. Recent literature suggests that metamizole can induce the CYP3A4 isoenzyme, which means that it could decrease the effectiveness of the metabolism of drugs such as some benzodiazepines, tramadol,

codeine, fentanyl, methadone, paracetamol and glucocorticosteroids.

Interactions with paracetamol

Paracetamol is metabolized by the 1A2 isoenzyme of P450 cytochrome. For this reason it should be cautiously co-administered with drugs which inhibit the activity of this isoenzyme. This is of special practical importance when co-administered with ciprofloxacin, erythromycin, fluvoxamine and ticlopidine. Paracetamol increases the kidney's elimination of prostaglandins and decreases plasma renin activity. Consequently, it may imitate the diuretic effect of loop diuretics.

Interactions with codeine

Codeine co-administered with hypnotics, tricyclic antidepressants, mianserin, mirtazapine, trazodone, benzodiazepines and neuroleptics has a synergistic depressive influence on the central nervous system. When simultaneously administered with other opioids, the risk of respiratory depression increases.

Codeine undergoes hepatic metabolism under the influence of the 2D6 and 3A4 isoenzymes of P450 cytochrome. For this reason, caution should be taken when co-administering drugs inhibiting the activity of the above-mentioned isoenzymes. Drugs of the most clinical importance with the capacity to inhibit CYP2D6 and CYP3A4 isoenzymes are presented in Table 3.

Interactions with tramadol

Tramadol undergoes hepatic metabolism under the influence of the CYP2D6 isoenzyme. As a

result, the pharmacologically active metabolite O-demethyl tramadol (M1) is formed. For this reason, the simultaneous administration of tramadol with drugs inhibiting the activity of CYP2D6 (Table 3) is not recommended: on the one hand it inhibits the formation of the active metabolite but on the other it may lead, especially when forms with prolonged action are used, to undesirable and even toxic symptoms. We must bear in mind that 5–10% of the Caucasian population slowly metabolize drugs with the CYP2D6 isoenzyme, and thus in these patients the risk of undesirable pharmacokinetic interactions is additionally increased. Tramadol, apart from its influence on opioid receptors, also inhibits serotonin reuptake in the descending antinociceptive system, which causes an increased risk of serotonin syndrome.

Caution should be taken when co-administering tricyclic antidepressants (amitriptyline in particular) and serotonin reuptake inhibitors (fluoxetine and paroxetine in particular), because while such a combination inhibits the metabolism of tramadol, it also increases the risk of seizure and serotonin syndrome.

The use of metoclopramide as an antiemetic during tramadol therapy is also unfavourable. Metoclopramide is a strong inhibitor of tramadol metabolism.

Tramadol increases the depressive action of hypnotics, benzodiazepine derivatives and neuroleptics on the CNS. When co-administered with neuroleptics, it may cause seizures. Using tramadol with hypotensive drugs increases the risk of hypotension [4].

Interactions with nefopam

Nefopam should not be used with tricyclic antidepressants because of the risk of hyperthermia, severe hypertension and arrhythmia. Nefopam inhibits serotonin and noradrenalin reuptake and for this reason increases the potency of cholinolytic and sympathomimetic drugs.

Reserpine-containing drugs (Normatens) inhibit the analgesic action of nefopam.

Drugs should be used cautiously with benzodiazepine derivatives, hypnotics and first-generation antihistamine drugs.

Interactions with buprenorphine

Buprenorphine increases the depressive influence of tricyclic antidepressants and neuroleptics on the CNS. Used with other opioids, it increases the risk of depression of the central nervous system. By decreasing saliva secretion, cholinolytic drugs may hamper sublingual administration.

Table 3. Drugs suppressing CYP2D6 and CYP3A4 activity

CYP2D6	CYP3A4
Metoclopramide	serotonin reuptake inhibitors:
Amitriptyline	fluoxetine, paroxetine, sertraline
Bupropion	Ciprofloxacin
Fluoxetine	Norfloxacin
Paroxetine	Clarithromycin
Venlafaxine	Erythromycin
Haloperidol	Ketoconazole
Risperidone	Itraconazole
Thioridazine	Anastrozole
Doxorubicin	Cisapride
Lanzoprazole	Diltiazem
Methadone	Methadone
Valproic acid	Methylprednisone
	Valproic acid
	Werapamil

Interactions with dihydrocodeine

Dihydrocodeine should be used cautiously in patients taking MAO inhibitors. In people with genetically determined rapid drug metabolism, simultaneous Quinidine administration decreases the analgesic effect of the drug.

Interactions with morphine

Morphine acts synergistically with drugs with a depressive action on the central nervous system. Morphine increases the action of anticoagulants. Morphine is metabolized by UDPG 2D7 and CYP2D6 isoenzyme of P450 cytochrome and its metabolism can be inhibited by CYP2D6 inhibitors (see Table 3). As a result of morphine metabolism, the risk of undesirable effects is increased [5].

Metoclopramide increases morphine absorption from the digestive tract and intensifies its sedative effect. Tricyclic antidepressants, clomipramine and amitriptyline in particular, cause the prolongation of the half-life of morphine. Morphine and cimetidine preparations should not be administered simultaneously because of the increased risk of respiratory depression, as cimetidine can inhibit morphine metabolism.

Caution should be taken when simultaneously administering morphine and benzodiazepines because this combination increases the risk of respiratory depression. This concerns the co-administration of morphine and alprazolam in particular, which introduces analgesic action via an opioid receptor of the mu type.

Interactions with fentanyl

Fentanyl increases the depressive influence of hypnotics on the CNS, sedatives, benzodiazepine derivatives and antihistamine drugs transferring to the CNS. Fentanyl is metabolized by the 3A4 isoenzyme and drugs which inhibit the activity of this isoenzyme can increase the risk of adverse drug reactions (see Table 3).

Interactions with methadone

Methadone is metabolized by the CYP 3A4 isoenzyme, hence caution should be taken when combining drugs inhibiting its activity (Table 3). Methadone metabolism inhibition may cause bradycardia, mood swings, depression of the respiratory centre and an increased risk of potentially lethal arrhythmia, which are linked to QT prolongation in ECG.

Methadone should be cautiously combined with benzodiazepine derivatives due to the significant

toxicity of this mixture and the increased risk of bradycardia, sleep disruption, depression, urinary retention and the depression of cough and respiratory centres.

Caution should also be used when co-administering methadone with tricyclic antidepressants (TCA) because methadone disturbs their metabolism, inhibiting the activity of the CYP 2D6 isoenzyme.

However, barbiturates, carbamazepine, rifampicin, risperidone and glucocorticosteroids suppress the analgesic action of methadone, probably because of interactions with CYP3A4.

Methadone may disrupt the metabolism of beta-adrenolytics, neuroleptics and weak opioids (codeine, dihydrocodeine, tramadol), increasing the risk of undesirable effects [6].

Interactions with ketamine

Ketamine increases the activity of myorelaxants. It should be co-administered cautiously with alpha and beta adrenolytics and calcium antagonists, benzodiazepine derivatives and opioids, due to the risk of heart failure.

Ketamine used with aminophyllin decreases the convulsant threshold.

Interactions with dextromethorphan

Dextromethorphan is metabolized with the CYP 2D6 isoenzyme and its use with drugs inhibiting the activity of this isoenzyme (Table 3) increases the risk of respiratory depression, nausea and dizziness.

Dextromethorphan intensifies the effects of sedatives, hypnotics, neuroleptics and benzodiazepine derivatives on the CNS structures.

Interactions with amantadine

Amantadine increases the undesirable effects of anticholinergic drugs, you need a conjunction here to link these statements cotrimoxazol decreases the renal clearance of amantadine, increasing the risk of undesirable effects. Hydrochlorothiazide increases plasma amantadine concentration.

Interactions with antidepressants used in pain pharmacotherapy

Of the antidepressants used in pain pharmacotherapy, tricyclic antidepressants, doxepin, mianserin, mirtazapine and venlafaxine have found clinical use.

The interactions with serotonin reuptake inhibitors (SSRIs) will not be discussed further in this paper, due to the minor importance of this group of

Table 4. Interactions with antidepressants

Drug/group of drugs	Interaction with other simultaneously administered drugs
Tricyclic antidepressants (TCA)	Amitriptyline and clomipramine, the most frequently used drugs from the TCA group, are metabolized with the participation of multiple isoenzymes of P450 cytochrome. Consequently, there is a significant risk of unfavourable pharmacokinetic interaction. Amitriptyline is metabolized by 2D6, 3A4, 1A2, 2C9 and 2C19 isoenzymes, and clomipramine with 3A4, 1A2, 2C19 isoenzymes. Drugs suppressing the activity of the above-mentioned isoenzymes will inhibit the metabolism of TCAs, increasing the risk of undesirable effects. TCAs may increase the potency of sympathomimetics, causing an increase in blood pressure. Due to the strong cholinolytic effect, TCAs inhibit peristalsis of the digestive tract and may thus impair the absorption of orally administered drugs. Clomipramine, the most serotonergic drug amongst TCAs, may be a cause of serotonin syndrome as a result of pharmacodynamic interaction with other drugs that increase serotonergic transmission.
Doxepine	Should not be co-administered with QT-prolonging drugs in ECG, as it increases the risk of potentially lethal arrhythmia. Doxepine increases the depressive action of other sedatives, anxiolytics, antidepressants and neuroleptics on the CNS.
Phenothiazine	neuroleptics increase the cholinolytic effect of doxepine.
Mianserin	Acts synergistically and depressively with anxiolytics, hypnotics and sedatives on the CNS.
Mirtazapine	Increases the sedative effect of benzodiazepine derivatives.
Venlafaxine	Metabolized by 2D6 and 3A4 isoenzymes of P450 cytochrome. Thus co-administration with drugs inhibiting activity of these isoenzymes (Table 3) should be avoided. Caution should be used in simultaneously administering venlafaxine with tramadol and other drugs of serotonergic effect due to an increased risk of serotonin syndrome.

Table 5. Interaction with anti-convulsants used in pain pharmacotherapy

Drug	Interaction with other simultaneously administered drugs
Valproic acid	Valproic acid increases plasma carbamazepine concentration, carbamazepine decreases plasma valproic acid concentration. Valproic acid increases the effect of antidepressants, neuroleptics and oral anticoagulants. If co-administered with clonazepam, idiopathic epilepsy may occur. Should be cautiously administered with drugs bearing a strong affinity for blood proteins, due to the ability to increase free drug fraction.
Carbamazepine	Drugs whose concentration increases after simultaneous administration with carbamazepine, leading to an increase in the risk of unfavourable effects: verapamil, diltiazem, fluoxetine and isoniazide. Carbamazepine may decrease the therapeutic effectiveness of oral anticoagulants, clonazepam, alprazolam, corticosteroids, cyclosporine, digoxin, doxycycline, oestrogens and gestagens. When co-administered with thiazides and/or furosemide, hyponatraemia may occur. Theophylline decreases plasma carbamazepine concentration. Carbamazepine acts synergistically with neuroleptics. However, it must not be forgotten that the risk of toxicity increases with such a combination.
Gabapentin	Hypnotics increase drowsiness and ataxia after gabapentin. Drugs from the antacid group decrease gabapentin absorption from the digestive system. Morphine increases gabapentin blood concentration.
Pregabalin	Increases the effect of lorazepam.

drugs as co-analgesics. Interactions with antidepressants that are important from a practical point of view are shown in Table 4 [7].

Interactions with anti-convulsants used in palliative care

Drugs of the greatest practical importance in pain pharmacotherapy with neuropathic components are valproic acid, carbamazepine, gabapentin and pregabalin. Interactions with these drugs are presented in Table 5.

tin and pregabalin. Interactions with these drugs are presented in Table 5.

Interactions with relaxants: hyoscine butylbromide, papaverine, drotaverine

The cholinolytic effect of hyoscine is increased by TCAs, benzodiazepines and neuroleptics. Hyoscine intensifies the effect of drugs causing CNS depression and suppresses the effect of dopamine

antagonists on intestinal peristalsis. Papaverine and drotaverine may intensify the effect of hypotensive drugs.

Interactions with neuroleptics

The most frequently used neuroleptics are haloperidol, levomepromazine and risperidone.

Interactions with haloperidol

Haloperidol increases the depressive action of opioids, benzodiazepines, barbiturates and TCAs on the CNS. Valproic acid and oral anticoagulants intensify the effect of haloperidol. Haloperidol increases the cholinolytic effect of other simultaneously administered drugs. It increases the action of hypotensive drugs, except clonidine to which it acts antagonistically.

As for hypotension in patients treated with haloperidol, catecholamines should not be used due to the risk of a paradoxical and further decrease of blood pressure. Haloperidol should not be co-administered with magnesium salts due to the risk of respiratory depression and hypotension.

Interactions with levomepromazine

Drugs of cholinolytic effect intensify the anticholinergic effect of levomepromazine. CNS depressing drugs, including opioids, co-administered with levomepromazine introduce a synergic suppressing effect on CNS functions. When co-administered with hypotensive drugs it can cause orthostatic hypotonia. Levomepromazine can induce unwanted drug interactions with procholinergic drugs such as metoclopramide.

Interactions with risperidone

Risperidone can increase the effect of drugs that have a depressing effect on the CNS. Carbamazepine decreases plasma risperidone concentration. TCAs and phenothiazines increase plasma risperidone concentration, increasing the risk of undesirable effects. A similar effect is observed in fluoxetine and paroxetine. Drugs in the form of oral solutions should not be drunk with tea and drinks such as Coca-Cola, because these drinks can decrease risperidone absorption from the gastrointestinal tract.

Interactions with glucocorticosteroids

Dexamethasone, methylprednisolone and prednisone are metabolized with CYP 3A4, which can be induced simultaneously by CYP 3A4 inducers. Glucocorticosteroids suppress the effect of oral anti-

diabetics and anticoagulants. Combined with NSAIDs, they increase the risk of bleeding in the upper part of the digestive tract. When co-administered with diuretics, they increase the loss of potassium ions.

Barbiturates and anti-epileptics decrease the effect of glucocorticosteroids.

Interactions with drugs used in the treatment of nausea and vomiting

Interactions with metoclopramide

Metoclopramide decreases (digoxin) or increases (NSAIDs, paracetamol, cyclosporine, levodopa) drug absorption from the digestive system. Due to its central action, metoclopramide intensifies the depressive action of benzodiazepine derivatives and TCAs on the CNS. It may increase opioid analgesia. Cholinolytic drugs decrease the effect of metoclopramide. Metoclopramide is a strong inhibitor of the 2D6 isoenzyme of P450 cytochrome and inhibits the metabolism of codeine and tramadol.

Interactions with thiethylperazine

Thiethylperazine increases CNS depression when co-administered with benzodiazepine derivatives and opioids.

Interactions with ondansetron, granisetron and tropisetron

These do not enter into clinically important interactions with other simultaneously administered medications.

Interactions with bisphosphonates (clodronate, pamidronate, zolendronate) and calcitonin

Bisphosphonates co-administered with glucocorticosteroids and calcitonin increase the risk of hypocalcaemia. Oral bisphosphonates given with NSAIDs increase the risk of damage to the upper part of the digestive tract.

Calcitonin does not interact with other simultaneously administered drugs.

Conclusion

As presented above, appropriate polytherapy is of key importance for pharmacotherapy in palliative medicine.

Prevention of unfavourable drug and post-drug interactions should be an inseparable element of responsible treatment.

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