Buprenorphine-induced acute respiratory depression during ifosfamide-based chemotherapy

Buprenorphine is a potent, semi-synthetic opioid analgesic derived from thebaine. The drug displays the characteristics of an agonist at the mu receptors and antagonist at the kappa receptors. Although buprenorphine has shown some pharmacological effects on delta and kappa opioid receptors, the action on the mu receptors appears to be responsible for most of the analgesic effects associated with this compound.

A new transdermal delivery system (TDS) has recently been introduced. This buprenorphine matrix patch is available in three doses, which releases 35, 52.5 and 70 µg/h, respectively; these rates correspond to daily doses of 0.8, 1.2 and 1.6 mg buprenorphine. Published data on the pharmacokinetic properties of buprenorphine administered by transdermal delivery system are limited [1].

A 34-year-old man with a partially resected osteosarcoma of the fronto-parietal skull and pelvic bone metastases entered our Oncology Unit. Ifosfamide 2 g/m² was administered once a day for 3 days as part of a sequential schedule also including doxorubicine, cisplatin and etoposide. In addition the patient received buprenorphine 35 µg/h to treat the pain.

On admission he presented with proximal right limb somatic pain (VNS 7) due to his pelvic localisation. Physical examination and laboratory values were in the norm. Codeine 60 mg once a day and paracetamol 730 mg once a day was given without relief. On the first day of chemotherapy he started therapy with transdermal buprenorphine 35 µg/h/72. During the following 24 h he did not obtain any relief from pain so the buprenorphine TDS dosage was increased to 52.5 µg/h. After 12 h he became confused and fell asleep easily. On medical examination he had a reduction of respiratory rate (from 20/min to 10/min), pupillary constriction and sinusal bradycardia (48 beats/min) on ECG.

The transdermal buprenorphine was removed and vital parameters were monitored every 30 min. Over the following 12 h the patient had a slight and constant improvement, and after 24 h made a complete recovery.

The efficacy of transdermal buprenorphine patches in treating chronic pain has been investigated in several multicentre randomised, double-blind placebo-controlled parallel group studies. Most of the enrolled patients had non-malignant pain. Only in one trial [2] do we know how many patients were receiving concomitant chemotherapy.

A high percentage of buprenorphine is bound to plasma protein and is metabolised in the liver by the cytochrome P450 3A4-enzyme system into norbuprenorphine and other products. Concomitant exposure to drugs that inhibit this enzyme may intensify the action of buprenorphine.

Ifosfamide is a bifunctional alkylating agent, used as a racemic mixture by the intravenous route in the treatment of...
various oncological diseases. It is an oxazaphosphorine derivative with a structural formula similar to that of cyclofosfamide. As a prodrug it requires activation in the liver by a cytochrome mixed-function oxidase system. Although there is no definite answer as to whether or not CYP3A4 is the only isoenzyme in the metabolism of ifosfamide in humans, both hydroxilation and dechloroethylation have been demonstrated to be mainly dependent on CYP3A4 activity. The metabolic pathway could become saturated when ifosfamide is used at a dose >16 mg/mq [3].

Since there is a common enzyme for ifosfamide and buprenorphine, which implies a potential for a pharmacokinetic drug interaction, we believe the chemotherapy with ifosfamide precipitated the respiratory depression due to concomitant interaction with cytochrome P450 3A4. In contrast to full mu agonist, overdose of buprenorphine (by itself) does not appear to cause lethal respiratory depression in non-compromised individuals. Most studies indicate long term but moderate respiratory depression, independent of the route of administration [4]. Studies comparing the respiratory effect of buprenorphine with that of morphine at equi-analgesic doses, show equal depression of ventilation, although the effects of buprenorphine last longer [5].

One recent study [4] presented strong evidence for the existence of a ceiling of buprenorphine in respiratory depression since buprenorphine displays slow opioid-receptor association and dissociation kinetics. This ceiling effect is best explained by its partial agonism at the mu-opioid receptor. This distinctive effect on respiratory effect contributed to the concept that buprenorphine is exceptionally safe.

In our patient, we did not administer naloxone and reversal of respiratory depression was obtained by removing the opioid patch and administering oxygen by mask.

This interaction suggests the need for future studies including cancer patients in active oncological treatment. Oncologists must be cautious due to the pharmacokinetic interaction between buprenorphine and chemotherapy agents metabolised by cytochrome P4503A4.

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