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Tramadol overdose: review of the literature

Intoxication au tramadol : mise au point

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Abstract In France, like in several other European countries, dextroproxyphene has been banned from the market in 2011. Consequently, a significant increase in tramadol prescriptions as well as a significant increase in tramadol overdoses and poisonings could be expected. Tramadol is a synthetic opioid responsible for numerous adverse effects in case of overdose, including life-threatening ones such as loss of consciousness, seizures, serotonin syndrome, and more rarely hypotension and cardiovascular failure. Such complications have been reported in Iran, where tramadol is largely abused among opioid-dependent drug users. Thus, a strict toxicological surveillance should be developed in France to prevent a possible increase in tramadol-related morbidity and fatalities among acute poisoned patients, as reported in Iran. ***To cite this journal: Réanimation 20 (2011).***

Keywords Tramadol · Poisoning · Seizure · Serotonin syndrome

Résumé La France, à l'instar de plusieurs autres pays européens, a décidé de retirer du marché en 2011 toutes les spécialités à base de dextropropoxyphène. De ce fait, une augmentation significative des prescriptions d'antalgiques à base de tramadol pourrait être observée, avec comme conséquence une augmentation des cas de surdosage et d'intoxication. Le tramadol est un opioïde de synthèse à l'origine de nombreux risques y compris vitaux pouvant conduire un patient intoxiqué en réanimation : troubles de la conscience, convulsions, syndrome sérotoninergique et plus rarement hypotension et état de choc. De telles observations ont largement été documentées en Iran, où ce médicament est à l'origine d'un détournement d'usage chez les consommateurs de drogues dépendants aux opioïdes. Une vigilance particulière doit donc être instaurée en France pour éviter que le tramadol ne conduise à son tour à un accroissement significatif de la morbimortalité des intoxications aiguës, comme déjà observé en Iran. ***Pour citer cette revue : Réanimation 20 (2011).***

Mots clés Tramadol · Intoxication · Convulsion · Syndrome sérotoninergique

Introduction

Recently, despite some scepticism, all pharmaceuticals including dextropropoxyphene were banned from the French market, as previously done in the United Kingdom (UK) and Sweden. Such a landmark European decision indicated that at last the toxicology of prescription drugs in overdose was being taken seriously within the drug regulatory community. Consistently, the combination of co-proxamol was shown to be 10 times more likely to cause death for every million prescriptions issued than the other compound paracetamol–opioid preparations with codeine and dihydrocodeine that are widely used in the UK [1,2]. Similarly, episodes of poisoning notified to the UK National Poisons Information Service were in proportion to prescription numbers, confirming that the differences in mortality were indeed related to excess toxicity rather than disproportionate use in overdose [1,3].

Thus, following its ban from the market, dextropropoxyophene replacement by tramadol, another level 2 analgesic according to the classification of the World Health Organization, is expected to strongly increase. Consequently, a significant increase in tramadol poisonings may be hypothesized, including severe cases admitted to the intensive care units. Tramadol-related toxicity is well known in Iran, where this pharmaceutical is largely abused among opioid-dependent drug users. The objectives of this article were to review the clinical features attributed to tramadol poisoning and to discuss its life-threatening risks in order to improve patient management.

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Pharmacology of tramadol: what should be known to understand toxicity

Tramadol, (1RS; 2RS)-2-[(9dimethylamino)-methyl]-1-(3-methoxyphneyl)-cyclohexanol hydrochloride, is a synthetic analogue of codeine [4,5]. Tramadol expresses a dual mechanism of action that includes weak agonistic effects at the μ-opioid receptor as well as inhibition of serotonin and norepinephrine reuptake [6]. Tramadol has two measured primary metabolites, N-desmethyl and O-desmethyl tramadol [7]. While the affinity of tramadol for μ-opioid receptors (analgesic effect) is 10-fold less than codeine, its active metabolite, O-desmethyl tramadol, has far greater affinity (up to 200-fold) [8] and twice the analgesic potency of the parent drug. The synergism of these effects contributes to tramadol's analgesic properties [9]. In addition to its low affinity to opioid receptors, tramadol inhibits the reuptake of norepinephrine and serotonin, producing an analgesic action by blocking nociceptive impulses in the spine [10,11]. Tramadol is structurally similar to venlafaxine, and therefore, may also act similarly to antidepressants [12,13].

After oral administration, tramadol is rapidly and almost completely absorbed [14]. Sustained-release tablets release the active ingredient over a period of 12 hours, reach peak concentrations after 4.9 hours, and have a bioavailability of 87–95%. Tramadol plasma protein binding is about 20%. Tramadol is distributed in blood, liver, kidney, and brain samples, but not muscles, according to postmortem studies [15,16]. Similarly to morphine, it is significantly accumulated in the bile in comparison to liver and kidney tissues. Tramadol's distribution is consistent with a volume of distribution of 3 l/kg [17]. Tramadol is mainly metabolised by O- and N-demethylation and by conjugation reactions forming glucuronides and sulfates. Tramadol and its metabolites are mainly excreted via the kidneys. The mean elimination half-life is about 6 hours. The O-demethylation of tramadol is catalysed by cytochrome P450 (CYP) 2D6, whereas N-demethylation is catalysed by CYP2B6 and CYP3A4. The wide variability in the pharmacokinetic properties of tramadol can partly be ascribed to CYP polymorphism.

Tramadol poisonings: main features and toxicity

Originally it was claimed that tramadol is rather safe and has low potential for abuse [5,18]. However, contradicting evidence has emerged in later stages. Food and Drug Administration has issued safety alert on this drug, including special cautions for patients who are simultaneously taking tranquilizers or antidepressants as well as individuals who consume alcohol excessively, or for those who suffer from emotional disturbances or depression. Potential misuse, abuse and diversion were also stressed [19]. Consistently, it has been recently suggested to place tramadol into the Schedule IV of the Controlled Substances Act [20].

Complications in tramadol overdose are disproportionately higher. Much of the toxicity in tramadol overdose appears to be attributable to the monoamine uptake inhibition rather than its opioid effects [18]. Frequency of the tramadol-induced complications is on the rise. Prescription on the Internet, initial marketing on safety, low potential for abuse and diversion as well as dextropropoxyphene withdrawal in hospital settings have been contributive on this issue [18,21,22].

Reported tramadol overdoses are dominantly intentional acute ingestions. The majority of cases become symptomatic within the first 4 hours of ingestion and manifestations washed-out in 24 hours. It is reported that up to 20% of cases need intensive care unit admission [18,23–25]. Tramadol overdose generally involve young adults with mean ages in the 20s [18,23–25]. Although less common in males (41 to 45%) according to poison centre studies [18,23], it is a male dominant problem in hospital settings (63 to 72%) [24,25].

Clinical findings

Central nervous system (CNS) manifestations are the most common reported symptoms to the hospitals, ranging from CNS depression (27 to 63%) to lethargy (30%) and deep coma (3 to 5%) [18,23–25]. In contrast, agitation is also reported in 10% of cases [18].

Seizures are a critical issue in tramadol poisonings. While population-based studies related to tramadol overdose reveals a frequency of seizure of 8% [18] to 14% [23], reports from hospitals are related to higher risk of seizure from 15% [24] to 35% [25]. It has been shown that, tramadol in either therapeutic or excessive doses during monotherapy or co-administrations particularly with antidepressants may lead to seizure [8,26,27]. Widely different frequency of seizure could probably be the result of these determinants. In single-use and appropriate doses, no increased risk of seizures in comparison to other analgesic monotherapies were reported [28,29]. According to population-based studies, less than one percent of these cases experience seizure [30]. In contrast, frequency of seizure was shown to be higher with medical comorbidities and concomitant prescribed drugs or in overdose [30]. A big chunk of new-onset seizures could be attributed to tramadol exposure [31]. Among 126 tramadol overdoses from seven poison control centers, 8% experienced brief seizures [18]. More than half (54%) of tramadol abusers reported at least one tonic-clonic seizure during a three-year study period [32]. In 83 cases of tramadol-associated seizures, half occurred in the presence of other

prescribed drugs; more than 50% of these co-administered drugs were antidepressants [33]. Case reports in regard to tramadol and antidepressants-induced seizure are common [27]. It has been thus recommended that concomitant prescriptions of tramadol with antidepressants, especially tricyclics or selective serotonin reuptake inhibitors (SSRIs) should be performed with caution [34], as these combinations may increase the risk of seizure.

The smallest amount of tramadol associated with seizure was reported to be 200 mg [23], 350 mg [24] or 500 mg [18]. The majority of seizures occurred within 6 hours of time of ingestion [23,24]. Tonic-clonic seizures followed by refractory convulsive status epilepticus have also been reported, although the frequency seems to be low [24,35].

Patients with mydriasis were shown to be at higher risk for seizure [23,24,36]. Although seizures were reported to be related to males, chronic use, intentional attempts, and tachycardia [23], these findings have not been confirmed in other studies [24,37]. Interestingly, the alleged ingested dose of tramadol, the respiratory rate, the presence of R waves greater than or equal to 3 mm in aVR on the electrocardiogram (ECG) as well as naloxone administration were not reported to be associated with seizures [24].

Miosis is not as common characteristics as with other commonly abused opioids. Only up to one-third of tramadol overdosed patients were observed to have a miosis [28]. This is probably related to the inhibition of norepinephrine and serotonin reuptake.

Nausea and vomiting have an incidence varying between 14 to 76% [18,23,25]. *Respiratory depression* was reported from 2 to 50% [18,24]. The lowest dose associated with respiratory depression was reported to be 800 mg [18].

Lower blood pressures particularly systolic and *sinus tachycardia* have been reported [18,23,24,27]. This is similar to the previous findings of other opioids [38,39]. In the majority of poisonings, no arrhythmias beyond tachycardia or serious cardiovascular toxicity were documented [24,38]. ECG indices and R wave/S wave in aVR were in particular not reported to be abnormal. However, cases with *Brugada ECG patterns, acute right heart failure, refractory shock and asystole* have been reported [27,40–46]. Surprisingly, *hypertension* has also been described [18].

Several other symptoms were reported in tramadol overdoses, sometimes in isolation and sometimes in association with others, including *vertigo, blurred vision, palpitation, hyporeflexia, diaphoresis, diplopia, and hyperreflexia* [25]. Multiple organ failure and severe acute liver failure due to fulminant hepatic necrosis were also described [45–47].

Serotonin syndrome

Serotonin syndrome (SS) has been reported with tramadol overdoses [8,18,24,43,48]. The exact incidence of tramadol overdose-induced SS remains unknown; however, it probably does not exceed 5 % in hospital settings [24]. SS may occur during single tramadol use, but it appears to be more common following either excessive use or overdose or with the co-administration of other medications, particularly antidepressants. No association was found between the frequency of SS and the alleged dose of tramadol overdose. Tramadol could have a synergistic effect on other drug-induced SS [49]. It may occur with tramadol monotherapy, but SS has been documented in combinations of tramadol and the following medications: citalopram [50], fluoxetine [51–53], fluvoxamine [54], moclobemide-clomipramine [49], mirtazapine [55], paroxetine [56–59], sertraline [60–62] and venlafaxine [63,64]. Interestingly, we are convinced that true rate of tramadol-induced SS might be even higher than currently reported, if agitation, tachycardia, confusion, and hypertension were considered as possible mild SS symptoms, which easily could be missed in clinical settings.

SS may develop via (i) excessive serotonergic agonism of serotonin receptors in the central and peripheral nervous systems or (ii) as a result of increased serotonin synthesis, (iii) decreased serotonin metabolism, (iv) increased serotonin release, (v) inhibition of serotonin reuptake (e.g. SSRIs), and (vi) direct agonism of serotonin receptors [65–67]. Tramadol, in addition to affecting μ-opioid receptors, stimulates pre-synaptic release of serotonin and inhibits serotonin reuptake [24,67]. Otherwise, SSRIs can inhibit the CYP2D6 isoenzyme metabolising tramadol, resulting in therapeutic overdose of tramadol and, in susceptible individuals, idiosyncratic induction of SS.

Biological features

Tramadol overdose may induce a rise of creatinine phosphokinase (CPK). Although CPK rise could be independent from seizure, in cases with seizure, CPK rise is more dramatic and may be associated to acute renal failure [33,38,44,45]. Increase in white blood cell count has been reported [24]. Bleeding risks due to tramadol interaction with oral anticoagulants has also been stated [68]. To date, there are no biological markers of SS and diagnosis remains to rely on the clinical presentation [69].

Tramdol-related fatalities

Tramadol overdose-induced deaths are rare and does not exceed 1% of admitted cases [7,10,24,46]. Death is more common in combination of tramadol and other drugs such as antidepressants and benzodiazepines [10,70,71]. Interpersonal variability in tramadol concentrations and a wide therapeutic concentration range exists in patients receiving tramadol [72]. Concentrations of 8 mg/l, 9.6 mg/l,

22.6 mg/l or 38.3 mg/l, which exceeded at least 30-times the normal therapeutic range of 0.1-0.3 mg/l, have been reported in fatal cases [9,16,46,71].

Specificities in children

Although adverse effects of tramadol in children at therapeutic doses are mild, they may happen more frequently and vomiting is especially more common [73]. Accidental ingestions in children are well tolerated, primarily causing sedation [23]. However, ingestions of more elevated doses may lead to significant toxicity. Cases with respiratory depression or SNC depression require admission to an intensive care unit [74]. Dystonia, seizures or seizure-like activities have also been reported [3,75].

Management of tramadol poisonings

Management should be focused on supportive treatments, including supplemental oxygen delivery, fluids, and diazepam to control agitation or seizure. Patients should also be monitored for CPK rise and potential acute renal failure, which could happen a couple of days later [44]. Some patients may require tracheal intubation and mechanical ventilation and thus be admitted into the intensive care unit [18,23–25]. Gastrointestinal decontamination should be limited to patients admitted within 2 hours after the ingestion and in the absence of any contra-indication. In severely poisoned patients following the ingestion of large quantities of slow-release presentations, multiple dose of activated charcoal should be considered, if not contra-indicated or if the patient is intubated. In exceptional severe cases, tramadol-related cardiovascular failure may result in refractory shock and asystole requiring extracorporeal life support to allow patient's survival [27].

Naloxone is able to reverse tramadol-induced agonist effects mediated via μ-opioid receptors. In particular, patients with sedation, respiratory depression, and apnea may benefit from naloxone [18,23,24]. The duration of naloxone administration might need to be long [76].

Co-ingestion of tramadol with other drugs and patients with mydriasis are more prone to seizure. These could be related to serotonin or adrenaline involvement. Perhaps empirical, early treatment with benzodiazepines in these cases may help patients with tramadol overdose even with no prior seizure [24]. Empirical benzodiazepines may also be helpful in cases with under-diagnosed mild SS.

Management of SS is supportive, with discontinuation of the serotoninergic agents and external cooling [69]. Up to 42% of patients may require admission to ICU, most of whom will recover over 12–24 h [67]. Antiserotonergic agents may be used, including oral cyproheptadine (a 5HT1A and 5HT2 receptor blocker) or parenteral chlorpromazine. Moreover, although discussed in the literature [69], the use of dantrolene could be questioned, as a recent publication suggested its interest in the management of 3,4-methylenedioxymethamphetamine-related SS [77].

Conclusions

Tramadol-related complications are on the rise, and this trend could be majored by dextropropoxyphene banning from the market. Potential tramadol abuse and diversion should not be underestimated. In low and middle income countries like Iran, where lack of law enforcement mechanisms is more widespread, limiting of accessibility to this medication and replacement with less harmful opioids would serve general population. A tight toxicological surveillance should be developed in France to prevent a possible increase in tramadol-related morbidity and fatalities among acutely poisoned patients, like we observed in Iran.

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