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The efficiency of a carbamazepine–mianserin combination scheme in opiate detoxification

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A recent comparative randomized double-blind study has suggested the utility of a carbamazepine/mianserin combination as a treatment for opiate withdrawal. The aim of the present study was to explore the feasibility and efficiency of this combination under naturalistic conditions. Five hundred and fifty mostly polysubstance abusing patients treated with a standardized scheme combining carbamazepine and mianserin were assessed with regard to deviations to the protocol, used comedications and retention in treatment.
Three hundred and sixty three patients (66.0%) received the carbamazepine/mianserin combination as specified by the standardized protocol. In 350 patients (63.7%) the whole 10 days was completed. The most frequently used p.r.n. medications were for anxiety (47.5%) and insomnia (54.5%).
The treatment of opiate withdrawal with a carbamazepine/mianserin combination scheme in an inpatient setting seems to be feasible and applicable with few adaptations to most patients, and may represent an interesting treatment option for multidrug users.

KEY WORDS — carbamazepine; anticonvulsant; mianserin; antidepressant; opiate withdrawal

INTRODUCTION

Two main pharmacological strategies for opiate detoxification are commonly used: (1) substitution with an agonist (or a partial agonist) and gradual tapering of the substitute; (2) abrupt discontinuation of opiates and the use of non-opiate medications to reduce withdrawal symptoms (American Psychiatric Association, 1995). Clonidine has for some time become the drug mainly used for the second strategy. It acts by stimulating midbrain alpha$_2$-adrenergic receptors, thereby reducing the noradrenergic hyperactivity of the locus coeruleus that accounts for many of the symptoms of opiate withdrawal. Its efficacy on withdrawal symptoms has, though, to be considered as unsatisfactory, as symptoms such as anxiety, restlessness, insomnia, muscular aching and craving may not respond. Moreover, the side effects of clonidine include insomnia, sedation and hypotension. Contraindications to the use of clonidine include acute or chronic cardiac disorders, renal or metabolic disease and hypotension. The use of clonidine in the management of opioid withdrawal being hampered by sedation and hypotension, alternative alpha$_2$-antagonists have been tested. Lofexidine has in some countries replaced clonidine as the preferred drug for this indication, mainly due to its lesser effect on blood pressure (Amato *et al.*, 2004). This drug is, however, still not available in many countries, such as in Switzerland. As clonidine-assisted detoxification can be administered only to a restricted number of patients, due to its side effect profile (American Psychiatric Association, 1995), there is thus an interest in developing other pharmacological strategies.

The use of anticonvulsants for the treatment of substance abuse is based on a preclinical rationale linking

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kindling with drug craving (Halikas and Kuhn, 1990). Besides data showing a moderating effect on cocaine and opiate consumption (Chatterjee and Ringold, 1999; Halikas *et al.*, 1992; Mendelson and Mello, 1996; Myrick *et al.*, 2001), they have also been proposed as treatment for withdrawal syndromes, most studies, however, concentrating on alcohol and benzodiazepine withdrawal (Bertschy *et al.*, 1997; Myrick *et al.*, 1998).

Among others, carbamazepine has been proposed repeatedly as withdrawal treatment for benzodiazepine detoxification. Following some encouraging preclinical studies (Martijena *et al.*, 1997) and initial positive case reports, in which alprazolam withdrawal-syndrome was attenuated by carbamazepine in adult (Klein *et al.*, 1986) and elderly patients (Swantek *et al.*, 1991), several open trials (Garcia-Borreguero *et al.*, 1991; Kaendler *et al.*, 1996; Ries *et al.*, 1989) and three double-blind placebo-controlled trials (Di Costanzo and Rovea, 1992; Klein *et al.*, 1994; Schweizer *et al.*, 1991) have established its utility in benzodiazepine withdrawal.

The drug has also received some attention in the treatment of alcohol withdrawal. An anticonvulsant effect of carbamazepine during alcohol withdrawal has been confirmed very early (Chu, 1979; Sternebring *et al.*, 1983) and has encouraged the evaluation of the substance as an alcohol withdrawal treatment. Furthermore, in preclinical studies (Strzelec and Czarnecka, 2001) carbamazepine diminished ethanol withdrawal symptoms in rats, and prevented the development of tolerance to the hypnotic effect of ethanol. Besides one open study (Stuppaeck *et al.*, 1990), and two open comparative trials (Franz *et al.*, 2001), several double-blind studies have compared carbamazepine with placebo (Bjorkqvist *et al.*, 1976; Hillbom *et al.*, 1989) or with other treatments (Flygenring *et al.*, 1984; Hillbom *et al.*, 1989; Malcolm *et al.*, 1989; Malcolm *et al.*, 2002; Ritola and Malinen, 1981; Stuppaeck *et al.*, 1992).

Mianserin, a presynaptic alpha$_2$ and postsynaptic 5HT$_2$ blocker has been shown to attenuate alcohol and opiate withdrawal signs in animal models (Kleven and Sparber, 1989; Lal *et al.*, 1993; Neal and Sparber, 1986), this effect having been related to its 5HT$_{2C}$ blocking properties (Lal *et al.*, 1993).

In a recent randomized double-blind study of a carbamazepine/mianserin combination against clonidine on 32 patients performed in Lausanne by Bertschy *et al.* (1997), there were no differences with regard to the intensity of the withdrawal, to the rate of retention in treatment, to symptoms or to psychic distress in opiate dependent patients.

As carbamazepine has been suggested until now as an alternative treatment for opiate detoxification as well as for benzodiazepine and alcohol withdrawal, it may be of some interest for multidrug dependent patients undergoing detoxification from different substances. The aim of the present study was to explore the feasibility and efficiency of this combination under naturalistic conditions including a large proportion of patients presenting with multidrug dependence.

METHODS

Setting

The study was carried out in the specialized 10-bed drug detoxification unit of the University Department of Adult Psychiatry of Lausanne. Five hundred and fifty patients were treated between January 1998 and March 2001 with a standardized scheme combining carbamazepine and mianserin, as developed and published by Bertschy *et al.* (1997). The prerequisites for hospitalization in the unit are, among others, the referral by a professional (physician, social worker etc.), a prehospitalization consultation, and a rehabilitative programme planned directly to follow hospitalization in the unit. The standard hospitalization duration planned is 10 days for heroin, and 14 days for methadone detoxification.

Treatment

After exclusion of contraindications for mianserin and carbamazepine (especially liver alterations such as active hepatitis and the risk of pharmacokinetic interactions) and signing informed consent the patients were treated with the carbamazepine/mianserin scheme as shown in Table 1. The doses of the prefixed scheme were increased or decreased in case of persistence of opiate withdrawal signs or side effects,

Table 1. The carbamazepine/mianserin scheme

Day	Carbamazepine 200 mg	Mianserin 60 mg
1	1-1-1	0-0-1
2	1-1-1	0-0-1
3	1-1-1	0-0-1
4	1-1-1	0-0-1
5	1-1-1	0-0-1
6	1-1-1	0-0-1
7	1-1-1	0-0-1
8	1-0-1	0-0-0
9	1-0-1	0-0-0
10	0-0-1	0-0-0

respectively. The maximum daily doses were set at 800 mg for carbamazepine and at 120 mg for mianserin. The non-extended release formulation of carbamazepine was used.

Comedication

For specific symptoms the following comedications were administered: tizanidine or tolperisone for myorelaxation; zolpidem, zopiclone or trimipramine for insomnia; ibuprofen or piroxicam for analgesia; metoclopramide or ondansetron against nausea and vomiting; olanzapine or promazine against anxiety or agitation.

Assessment

Based on a standardized investigator submitted questionnaire, a semistructured interview was carried out at admission. Besides sociodemographic data, it examines drug consumptions, social background, medical and psychiatric history and legal status. The questionnaire was completed at discharge of the patient with, among others, data on hospitalization duration, treatment completion and adaptations of the carbamazepine/mianserin protocol, if it occurred. A urine drug screening was performed at admission.

RESULTS

Characteristics of patients

Of the 550 patients consecutively admitted to the unit and treated with the carbamazepine/mianserin combination, 397 (72.2%) were male. The mean age was 29.5 ± 6.5 years, and the mean duration of illegal drug abuse was 9.2 ± 11.0. Four hundred forty seven (81.3%) were admitted for heroin detoxification, 335 (60.9%) for methadone, 237 (43.1%) for cocaine, 29 (5.3%) for other stimulants, 238 (43.3%) for benzodiazepine abuse and 232 (42.2%) for cannabis. Whereas alcohol dependence alone is not an indication for admission to the unit, those patients being hospitalized in a specialized alcohol withdrawal clinic, 137 (24.9%) of the study patients presented a comorbid alcohol dependence, requiring therefore specific care for this problem. The mean hospitalization duration was 9.3 ± 5.3 days (range 1–29).

Treatment

The doses of the standardized scheme were increased or decreased in the case of persistence of opiate withdrawal signs or side effects, respectively.

With regard to the adherence to the protocol, 363 patients (66.0%) received the carbamazepine/mianserin combination as specified by the standardized protocol. For 177 patients (32.2%), the carbamazepine doses had to be adapted. Dose reductions of carbamazepine were performed for 159 (28.9%) patients at least once during the treatment, 13 patients (2.4%) had received at least one extra dose.

With regard to mianserin, 31 patients (5.6%) had their dose adapted at least once. There were 13 (2.4%) patients, for whom the dose had been augmented, and 18 (3.3%) for whom at least one dose was skipped.

Retention in treatment

Two hundred seventy two patients (49.5%) remained hospitalized as long as initially planned, and 78 (14.2%) left the unit prematurely, but after completion of the whole 10-day medication scheme. In 28 patients (5.1%) the treatment was suspended due to illegal drug consumption, and 172 (31.3%) left the unit prematurely against medical advice.

Concomitant treatment

Anxiolytic treatment was given p.r.n. at least once to 261 (47.5%) patients, 300 (54.5%) received hypnotics, 160 (29.1%) were given analgesics, 305 (55.5%) had at least once myorelaxant treatment and 66 (12.0%) received antiemetics.

Due to psychiatric comorbidity 67 (12.2%) entered the detoxification unit taking an antidepressant or were introduced to a long-term antidepressant treatment. Eighty-one (14.7%) of the patients had a long-term treatment with antipsychotic drugs, which was most often used as an anxiolytic in order to avoid benzodiazepines.

DISCUSSION

The efficacy of a carbamazepine/mianserin combination in the treatment of opiate withdrawal syndrome has recently been suggested (Bertschy *et al.*, 1997). The present study indicates a good applicability of the scheme in multidrug abusers in every day practice. In two thirds of the patients no dose adaptations were necessary. Most adaptations were carbamazepine reduction or skipped doses. Combining the carbamazepine/mianserin scheme with p.r.n. medications permitted the relief of even transitory symptoms of insomnia, muscle spasms and anxiety.

The completion rate of about 50% seems to be rather low at first sight. However, one has to consider the high percentage of multidrug use, and especially the proportion of 43% of cocaine consumers. Cocaine has repeatedly been shown to be associated with poorer treatment outcome (Broers *et al.*, 2000; Downey *et al.*, 2000).

Whereas these data confirm the interest of using carbamazepine and mianserin in this indication, the mechanism of action remains to be elucidated.

Several neurotransmitter systems have been implicated in opiate withdrawal including the dopaminergic, cholinergic, glutamatergic and noradrenergic systems.

The activation of noradrenergic cells in the locus coeruleus plays an important role in the symptoms of opiate withdrawal, as has been shown by biochemical, behavioral and electrophysiological studies (Rasmussen, 1995). Nordrenergic neurons send extensive projections throughout the CNS, including the cerebral cortex, hippocampus, cerebellum and spinal cord. A high density of mu and kappa opiate receptors has been found in the locus coeruleus and locus coeruleus neurons may be inhibited by the local or systemic administration of opiates. On the other hand, opiate antagonists, which precipitate withdrawal, increase norepinephrine turnover and release in locus coeruleus projection areas. The systemic administration and local infusion into the locus coeruleus of clonidine, an alpha$_2$-receptor agonist, suppresses the increased noradrenaline turnover as well as many behavioral symptoms seen during opiate withdrawal. Several anticonvulsive mechanisms of action have been described for carbamazepine (Kwan *et al.*, 2001). It stabilizes Na^+ channels in a voltage-, frequency- and time-dependent form, inhibits the rise in intracellular free Ca^{2+} induced by NMDA and can block the release of glutamate, but, interestingly, it has also been shown to increase the alpha$_2$-autoreceptor sensitivity to clonidine (Dilsaver *et al.*, 1993).

The nucleus accumbens, an essential structure associated with the development of addictive behavior, receives serotonergic input from the raphe nuclei. The firing rate of dopamine neurons is inhibited by 5HT$_{2C}$ receptor agonists, whereas the basal firing rate and the bursting activity of dopamine neurons is increased by 5HT$_{2C}$ antagonists (Di Giovanni *et al.*, 1999; Di Matteo *et al.*, 2000). The 5HT$_{2C}$ blocking properties of mianserin have been shown to be associated with the prevention of anxiogenic behavior in rats during ethanol withdrawal (Lal *et al.*, 1993).

Mianserin also blocks the presynaptic alpha$_2$ receptor and, in doing so, acutely enhances the release of noradrenaline. Alpha$_2$ adrenergic receptor antagonists such as idazoxan have been shown to increase the locus coeruleus firing, and some noradrenergic antidepressants decrease the firing when chronically administered. It can therefore be hypothesized that mianserin will decrease locus coeruleus activity after repeated administration.

Other anticonvulsant drugs have recently been suggested as a treatment for substance withdrawal. Gabapentin has been used for alcohol withdrawal (Bonnet *et al.*, 1999; Bozikas *et al.*, 2002; Myrick *et al.*, 1998; Watson *et al.*, 1997), phenobarbital for opiate withdrawal in neonates (Coyle *et al.*, 2002), valproate for benzodiazepine (Harris *et al.*, 2000; Rickels *et al.*, 1999) and alcohol (Longo, 2000) withdrawal. With regard to opiate detoxification, lamotrigine (Rosen *et al.*, 1998) and topiramate (Krenz *et al.*, 2002; Zullino *et al.*, 2002) are two drugs of the last generation which seem particularly promising.

In conclusion, the treatment of opiate withdrawal with a carbamazepine/mianserin combination scheme in an inpatient setting seems to be feasible and applicable with few adaptations to most patients. As most of these patients were polysubstance abusers, including alcohol and benzodiazepine dependence, the scheme seems to be an interesting treatment option for multidrug users covering their multiple needs.

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