Abstract
In this issue of Critical Care, Megarbane and colleagues present a case report of methadone-induced respiratory depression and conduct a toxicokinetic/toxicodynamic evaluation. An opioid-dependent patient receiving methadone maintenance treatment (daily dose 70 mg) was found unconscious after ingesting 240 mg methadone and 2 mg flunitrazepam. Significant improvement in consciousness was achieved after an intravenous bolus of 0.3 mg naloxone followed by a continuous infusion of naloxone at 0.3 mg/hour. In patients receiving methadone maintenance treatment, an occasional intake of two to four times the usual daily dose of methadone is not an exceptional occurrence. However, few such patients experience episodes of life-threatening respiratory depression. Here, we discuss whether recent pharmacogenetic data could help us to understand interindividual variability in sensitivity to respiratory depression and, ultimately, to predict which patients are most likely to be affected.

The case report by Megarbane and colleagues [1] reminds us that full tolerance to the opioid effects of methadone may never fully develop, even after long-term methadone maintenance treatment. Thus, even in tolerant patients, intake of a dose that is too high, up-titration of methadone dosage that is too rapid, or introduction of strong inhibitor(s) of methadone metabolism could cause life-threatening respiratory depression [2]. Interestingly, the maximal observed (R,S)-methadone plasma concentration (1204 ng/ml) in this case report is not, as stated, three times higher than peak levels in patients treated with a daily dosage in excess of 80 mg (mean dose ± standard deviation: 134 ± 82 mg/day, n = 209) [3]. Actually, it is only 68% higher than the mean peak (R,S)-methadone concentration (715 ± 395 ng/ml) and half the highest measured peak (R,S)-methadone concentration [3].

There are many factors that can contribute to the interindividual variability in sensitivity to respiratory depression following intake of a high dose of methadone in tolerant patients. Simultaneous intakes of other central respiratory depresssing agents such as benzodiazepines and alcohol are important risk factors [2]. The case report gives no indication as to whether alcohol was also used by the patient, although screening of blood for benzodiazepines, opiates, buprenorphine, cocaine and tetrahydrocannabinol was negative except for methadone [1]. The patient declared that the only other substance taken with methadone was 2 mg flunitrazepam. If this was true, then it is unlikely that this small quantity of flunitrazepam, in a patient who already had a history of occasional use of this benzodiazepine, could be a major factor contributing to the episode of respiratory depression.

In recent years interest in pharmacogenetic studies has grown; these studies aim to achieve a better understanding of interindividual variability in the response to treatment. Some tentative explanations for this variability might come from both pharmacokinetic and pharmacodynamic lines of inquiry. At the pharmacokinetic level, the first factor to consider is the enzymes that are involved in the metabolism of methadone, which is mainly mediated by cytochrome P450 (CYP)2B6 and CYP3A4, with a minor contribution from CYP2D6 [4]. CYP2B6 exhibits stereoselectivity toward the (S)-enantiomer of methadone [4,5,6], which is almost inactive as a µ-opioid receptor agonist [2]. In contrast, CYP3A4 is not stereoselective [4] and CYP2D6 could be stereoselective toward the active form of methadone, namely (R)-methadone [5,6]. It has been demonstrated that activity of these enzymes can be impaired as a result of genetic [4] and environmental (for example, inhibition of their activity by comedication and/or diet) factors. However, low metabolic activity cannot be proposed as an explanation for the episode of respiratory depression in the case described by Megarbane and colleagues [1].

CYP = cytochrome P450; PGP = permeability glycoprotein.
colleagues [1] because a short half-life for both enantiomers of methadone was measured, suggesting rapid metabolism.

A second factor that possibly contributes to interindividual sensitivity to methadone is the permeability glycoprotein (PGP), which is a transmembrane efflux transporter expressed in various human tissues, including intestine, liver and blood-brain barrier [7]. Genetic polymorphisms have been described for PGP that can contribute to differences in blood concentrations of methadone [4]. More importantly, a major role for PGP in limiting access of xenobiotics to the brain has been demonstrated in vivo in PGP-deficient mice, with little influence on blood concentrations [8]. Interindividual variability in PGP activity is therefore a strong candidate in genetically mediated sensitivity to methadone-induced respiratory depression. Another factor that may be involved in methadone pharmacokinetics is the strong blood binding of methadone to plasma proteins, in particular to α1-acid glycoprotein, which could significantly alter methadone pharmacokinetics [2]. However, despite the presence of genetic polymorphisms in α1-acid glycoprotein and differential binding of methadone to its variants [9], it is presently not possible to determine whether and to what extent this could influence sensitivity to respiratory depression.

At the pharmacodynamic level the most interesting factors are genetic polymorphisms described for the μ-opioid receptor, in particular the 118A>G single nucleotide polymorphism at exon 1 of the OPRM1 gene. In vitro, the variant protein has been demonstrated to exhibit three times greater binding affinity for the endopeptide β-endorphin, whereas binding to substances such as morphine, fentanyl, methadone and naloxone were unaffected [10]. However, in vivo, (R)-methadone had 1.74 times lower iotic potency (P<0.001) in carriers of the variant 118G allele as compared with noncarriers [11]. In addition, alfentanil concentrations that were two to four times greater were needed in homozygous carriers of the 118G allele as compared with wild-type subjects to produce the same degree of analgesia, and 10 to 12 times higher alfentanil concentrations were needed to produce the same degree of respiratory depression [12]. This suggests an important difference in sensitivity to respiratory depression depending on whether the 118A>G single nucleotide polymorphism is present. It should be noted that although genetic polymorphism in the μ-opioid receptor appears an interesting candidate for contributing to interindividual variability in sensitivity to opioid agonist induced respiratory depression, caution should be exercised when extrapolating the data from these single-dose studies to cases of overdose in tolerant patients. However, the 118A>G polymorphism in the human μ-opioid receptor gene also affects response to treatment after multiple doses as well, because cancer patients homozygous for the 118G allele need higher morphine doses to achieve pain control [13].

In summary, studies are needed to elucidate the interindividual variability in sensitivity to respiratory depression among opioid-dependant patients receiving methadone maintenance treatment. In this regard, genetic polymorphism in CYP isozymes, PGP and the μ-opioid receptor would be interesting factors to consider in future investigations.

Competing interests
The authors declare that they have no competing interests

References
1. Megarbane B, Declèves X, Bloch V, Bardin C, Chast F, Baud F: Case report: quantification of methadone-induced respiratory depression using toxicokinetic/toxicodynamic relationships. Crit Care 2007, 11:R5.
2. Eap CB, Buclin T, Baumann P: Interindividual variability of the clinical pharmacokinetics of methadone: Implications for the treatment of opioid dependence. Clin Pharmacokinet 2002, 41:1153-1193.
3. Crettol S, Déglon JJ, Besson J, Croquette-Krokkar M, Gothuey I, Hämig R, Monnat M, Hüttemann H, Baumann P, Eap CB: Methadone enantiomer plasma levels, CYP2B6, CYP2C19 and CYP2C9 genotypes, and response to treatment. Clin Pharmacol Ther 2005, 78:593-604.
4. Crettol S, Déglon JJ, Besson J, Croquette-Krokkar M, Hämmig R, Gothuey I, Monnat M, Eap CB: ABCB1 and cytochrome P450 genotypes and phenotypes: influence on methadone plasma levels and response to treatment. Clin Pharmacol Ther 2006, 80:668-681.
5. Begre S, von Bardeleben U, Ladewig D, Jaquet-Rochat S, Cosendai-Savary L, Powell Golay K, Kösler M, Baumann P, Eap CB: Paroxetine increases steady-state concentrations of (R)-methadone in CYP2D6 extensive but not poor metabolizers. J Clin Psychopharmacol 2002, 22:211-215.
6. Eap CB, Berstchy G, Powell K, Baumann P: Fluvoxamine and fluoxetine do not interact in the same way with the metabolism of the enantiomers of methadone. J Clin Psychopharmacol 1997, 17:113-117.
7. Marzolini C, Paus E, Buclin T, Kim RB: Polymorphisms in human MDR1 (P-glycoprotein): recent advances and clinical relevance. Clin Pharmacol Ther 2004, 75:13-33.
8. Schinkel AH, Wagenaar E, Mol CA, van Deemter L: P-glycoprotein in the brain-blood barrier of mice influences the brain penetration and pharmacological activity of many drugs. J Clin Invest 1996, 97:2517-2524.
9. Eap CB, Cuendet C, Baumann P: Binding of d-methadone, l-methadone, and d,l-methadone, and to proteins in plasma of healthy volunteers: role of the variants of alpha1-acid glycoprotein. Clin Pharmacol Ther 1990, 47:339-346.
10. Bond C, LaForge KS, Tian M, Melia D, Zhang S, Borg L, Gong J, Schluger J, Strong JA, Leal SM, et al.: Single-nucleotide polymorphism in the human mu opioid receptor gene alters b-endorphin binding and activity: possible implications for opiate addiction. Proc Natl Acad Sci USA 1998, 95:9608-9613.
11. Lötsch J, Skarke C, Wieting J, Oertel BG, Schmidt H, Brockmöller J, Geisslinger G: Modulation of the central nervous effects of levomethadone by genetic polymorphisms potentially affecting its metabolism, distribution, and drug action. Clin Pharmacol Ther 2006, 79:72-89.
12. Oertel BG, Schmidt R, Schneider A, Geisslinger G, Lötsch J: The mu-opioid receptor gene polymorphism 118A>G depletes alfentanil-induced analgesia and protects against respiratory depression in homozygous carriers. Pharmacogenet Genomics 2006, 16:625-636.
13. Klepstad P, Rakvat TT, Kaasa S, Holte M, Dale O, Borghgrevink PC, Baar C, Viken T, Krokan HE, Skorpen F: The 118 A>G polymorphism in the human mu-opioid receptor gene may increase morphine requirements in patients with pain caused by malignant disease. Acta Anaesthesiol Scand 2004, 48:1232-1239.