Suivi thérapeutique de la buprénorphine haut dosage et surveillance de l'observance

Therapeutic drug monitoring of high-dose buprenorphine : why and how ?

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Cet article est publié simultanément dans les Annales de Toxicologie Analytique et les bulletins de la Society Of Forensic Toxicologists (SOFT), de The International Association of Forensic Toxicologists (TIAFT), de la Gesellschaft für Toxikologische und Forensische Chemie (GTFCh) et de l'International Association of Therapeutic Drug Monitoring and Clinical Toxicology (IATDMCT), en accord avec les auteurs et les Rédacteurs en Chef.
(Reçu le 25 octobre 2004 ; accepté le 16 novembre 2004)

RÉSUMÉ

La buprénorphine est un opioïde semi-synthétique utilisé à hautes doses depuis 1996 en France pour le traitement de substitution des pharmacodépendances majeures aux opiacés. Aucune étude à ce jour n'a tenté d'établir l'intérêt du suivi thérapeutique pharmacologique (STP) de la buprénorphine haut-dosage. Le STP en général a essentiellement pour but de diminuer la fréquence des échecs thérapeutiques liés à une mauvaise observance ou à une dose insuffisante, et celle des effets indésirables liés à une dose excessive. Après une rapide revue des méthodes analytiques, en particulier immunochimiques, pour le dosage de la buprénorphine dans les liquides biologiques, cet article décrit les causes pharmacocinétiques et pharmacodynamiques probables de la faible relation concentration sanguine - effets observés à l'échelle d'une population et l'intérêt de la recherche urinaire et capillaire de la buprénorphine, mais aussi des autres opiacés, pour documenter respectivement l'observance et l'efficacité du traitement (la présence d'autres opiacés signant une efficacité imparfaite). En conclusion, le STP de la buprénorphine semble présenter peu d'intérêt, sauf cas d'inefficacité inexpliquée ou d'intoxication suspectée, contrairement aux recherches toxicologiques de buprénorphine, de son principal métabolite, de morphine et de ses dérivés.

MOTS-CLÉS

buprénorphine, suivi thérapeutique pharmacologique, opiacés, pharmacocinétique, cheveux.

SUMMARY

Buprenorphine is a semi-synthetic opioid, prescribed at high dose in France since 1996, as a maintenance therapy for opiate addicts. No study has addressed the potential usefulness of therapeutic drug monitoring (TDM) for high-dose buprenorphine so far. TDM general aims are to decrease the treatment failure rate linked to poor observance or underdosing and the incidence of adverse events due to overdosing. After a brief review of the analytical methods, particularly immunoassays, developed for the determination of buprenorphine in biological matrices, this paper describes the pharmacokinetic and pharmacodynamic causes of the weak blood concentration - effect relationships observed in the population and the use that can be made of urine and hair screening for buprenorphine and other opiates, in order to retrospectively document compliance and treatment efficacy (in terms of abstinence from morphine derivatives). In summary, TDM is apparently of little use for high-dose buprenorphine, except in case of unexplained inefficiency or suspected toxicity, contrary to toxicological screenings for buprenorphine, its main metabolite, morphine and its derivatives.

KEY-WORDS

buprenorphine, therapeutic drug monitoring, opiates, pharmacokinetics, hair.

Introduction

Buprenorphine (BU) is a semi-synthetic opioid derived from thebaine, an alkaloid of the poppy *Papaver somniferum*. It was first synthesized in the U.S.A. in 1973 by Alan Cowan and John Lewis, who also described its main properties, including its potential efficacy as a substitution treatment for heroin (1). High-dose buprenorphine (HD-BU) received approval as a substitution treatment for heroin addicts in 1996 in France and more recently in Australia, Germany and the USA. There are more than 70 000 ex-drug-addicts treated with this drug (Subutex®) in 2003 in France, and many others abuse this substance either sublingually or intravenously, often after buying it in the street. In France, HD-BU is available as sublingual tablets of 0.4 mg, 2 mg and 8 mg and the recommended administration scheme is once daily, based upon the duration of the psychotropic effects of buprenorphine, which are linked to the stability of the buprenorphine-receptor complex rather than to buprenorphine pharmacokinetic properties (2).

The question of whether or not this largely prescribed drug could benefit from therapeutic drug monitoring deserves to be addressed. Two major goals have been traditionally assigned to TDM, namely decreasing the treatment failure rate linked to poor compliance or to insufficient dosing and decreasing the frequency of side effects or toxicity linked with excessive dosing. The drugs that require (or benefit from) TDM generally present :

- Concentration-effects (either therapeutic or toxic effects) relationships stronger than the respective dose-effects relationships.
- A pharmacological response hardly accessible through effect measurement.
- A large inter-individual variability of the dose-concentration relation.
- A moderate or low short-term intra-individual variability of the same relationship (unless any forecasting attempt would be useless).
- A low therapeutic index (i.e. a narrow therapeutic range). The US Food and Drug Administration, gives it a narrow therapeutic range as the LD50 is less than twice the effective dose (3) requiring regular monitoring to minimize toxicity.

It is implicit that a suitable analytical technique is available for the drug of interest and possibly active metabolites.

As far as BU is concerned, very high doses were administered during clinical studies in humans with virtually no side-effects. Indeed, buprenorphine exhibits a very high affinity and a very long binding half-life with opioid μ -receptors. It is only a partial agonist for these receptors, meaning that its maximal effect is lower than that of morphine. This is called a "ceiling effect" (4). Consistent with the slow rate of receptor phosphoryla-

tion, the development of tolerance seems very slow and is often clinically insignificant. Withdrawal syndromes are generally late and of moderate intensity. However, BU pharmacokinetics shows a high inter-individual variability (5-7), which can be mainly explained by the genetic and phenotypic variability of the enzymes involved in its metabolism. It is mainly metabolized in the intestinal wall and the liver by a dealkylation reaction catalyzed by cytochrome P450 3A4, leading to norbuprenorphine (NBU), then by glucuronidation of BU and NBU. CYP 3A4 can be inhibited or induced by food, beverages and above all drugs. Also, several UDP-glucuronosyl-transferases were found to be coded by polymorphic genes giving rise to more or less active proteins.

In this paper, we will review further the clinical usefulness and feasibility of HD-BU dose adjustment and patients' compliance monitoring through the determination of buprenorphine in biological matrices, as well as of the monitoring of treatment efficacy in terms of documented abstinence from other opiates or psychoactive drugs, using urine and hair testing (compliance and efficacy monitoring being regarded here as part of TDM). We will not address HD-BU-related fatalities, which were already the subject of several papers (8-11).

Analytical methods for the determination of buprenorphine

Few immunoassays for buprenorphine (BU) determination in biofluids have been developed. The oldest one is a radio-immunoassay (RIA) in which the BU molecules in the sample compete with radio-labeled BU* for anti-BU antibodies (DPC, Los-Angeles, CA, USA). After incubation, separation and precipitation, the part linked to the antibodies is quantitated using a gamma counter (12). The lower limit of quantitation (LLOQ) of this technique is 1 ng/ml, which can be insufficient to measure the serum concentrations actually found in some patients. More recently, a microplate immunoassay (Cozart Biosciences Ltd, Abingdon, U.K.) has been commercialized for the semi-quantitative screening of BU in urine (with a LLOQ of 1 ng/ml) and serum (LLOQ = 0.5 ng/ml). The last released immunoassay is a purely qualitative microplate ELISA technique (Diagnostix Ltd, Mississauga, Canada, commercialized by Microgenics, Fremont, CA, USA) that can be used with a microplate reader as well as by direct visual reading by comparison with a control. Its LLOQ is 0.5 ng/ml in urine by visual reading.

Many chromatographic techniques were proposed for

the determination of BU and its metabolite norbuprenorphine (NBU) in biological matrices, from HPLC with coulometric detection (12), liquid chromatography-mass spectrometry coupling (LC-MS) (13,14), and gas chromatography - mass spectrometry (GC-MS) (12,14). Mass spectrometry is very often used as it fulfills the requirement of specificity necessary for forensic investigations (unexplained deaths, buprenorphine abuse, etc.), and because of its high sensitivity, very useful for the determination of this low-concentration drug. Most of the methods employing mass spectrometry yielded LLOQ between 0.1 ng/ml (13) and 0.5 ng/ml (14). One peculiarity of treatments with HD-BU is that their efficacy can be checked using toxicological analyses, most often by screening urine samples for drugs of abuse using immunoassays then confirming the positive samples with mass spectrometry.

HD-BU therapeutic drug monitoring and compliance checking in practice.

Determination of buprenorphine and metabolite in serum or plasma samples

There is a large inter-individual variability of the dose-concentration relationship of buprenorphine (5-7), which is a criterion in favor of the therapeutic drug monitoring of this drug, but the concentration-effects relationships and therapeutic range of HD-BU in human have not been clearly established. Buprenorphine is largely distributed in the body organs and tissues (as shown by its rather large distribution volume of about 2.5 L/kg), in particular in fat tissues such as the central nervous system where concentrations are higher than in blood. On the other hand, in humans buprenorphine effects are limited when the dose is increased ("ceiling effect"), whereas in animals and for even higher doses, its effects can decrease when the dose per body weight is increased even further ("inverted U curve"). BU also presents persistent effects after dosing, even after the blood concentration has drastically decreased (so-called "post-dose effect"), owing to its prolonged binding with the opiate receptors (fixation half-life of approximately 40 minutes, versus milliseconds for morphine). These phenomena can contribute to the poor correlation found in patients between BU serum levels and its clinical effects (whereas this relationship is better in a given individual). Also, HD-BU is administered to individuals with very diverse tolerance to opiates that can be attributed to both polymorphism and a variable desensitization of the opiate receptors, meaning that a very large range of doses (and concentrations in the vicinity of the receptors) are needed to produce the same effect.

This, in turn, contributes to the large inter-individual variability of this drug, as well as to the difficulty of establishing therapeutic ranges or concentration-effects relationships for opiates in populations of drug addicts or patients under maintenance treatment. However, the serum concentration values usually found at steady state are in the 1-10 ng/ml range in a majority of patients treated with HD-BU.

The serum or plasma determination of BU with the aim of fine dose adjustment would thus be ineffective and useless in most instances, even for the prevention of pharmacokinetic drug-drug interactions. In contrast to methadone no drug interactions have so far been reported for buprenorphine. Serum or plasma analyses are mainly useful for assessing treatment compliance and for the detection of drug abuse (such as by injection of crushed sublingual tablets) in the living and post-mortem.

Determination of buprenorphine and metabolite in urine samples

The long elimination half-life of BU limits drug compliance monitoring based on the urine or serum screening for BU and its metabolites. Clinical trials have shown that blood and urine concentrations were almost similar after administrations every other, or every fourth day and concentrations were proportional to dose (15).

On the other hand, as for methadone urine screens 2 or 3 times a week would be necessary to assess actual abstinence to other opiates, at least during the first 3 months of treatment, which would be very costly. In France such urine screens are performed much less frequently. Moreover, urine screens are limited as it only provides qualitative results, i.e. the presence or absence of BU or other opiates, contrary to hair analysis. However, urinalysis benefits from the existence of commercial immunoassays (such as those described above for BU), which can be run on biochemistry analyzers.

Determination of buprenorphine and metabolite in hair

Adult humans have approximately 5 million hair follicles, of which 1 million on the scalp give rise to hair. Hairs growth follows a three-phase cycle : growth or anagen phase (4 to 8 years), transition or catagen phase (2 weeks) and release or telogen (3 months). At any given time, about 85 % of hair is in the anagen phase. Vertex hair grows by 0.44 mm per day on average, i.e. 1 to 1.3 cm per month, with extremes of 0.7 to 1.5 cm/month (16).

The widely accepted mechanism for xenobiotic incorporation in hair is that of internal diffusion from blood into developing hair follicles, as well as external diffusion from sweat and sebaceous secretions into the hair shaft. Smoke particles in the atmosphere contaminated

with nicotine, cannabis or cocaine can potentially also deposit on the hair surface. This is the reason why efficient external decontamination must always be performed before any analysis (17). The stability of xenobiotics incorporated in hair is exceptional. A lock of approx. 60-80 hairs are cut with scissors near the scalp then orientated using a thin cord 1 cm above the root-end. Hair collection is easy and can be performed publicly without infringement of privacy, contrary to urine collection. There are very few refusals from the patients for such sampling. Also, hair samples cannot be adulterated as easily as urine and it is generally possible to obtain *a posteriori* a second, identical sample covering the time period under investigation. Hair storage is easy, as it only requires dry tubes or envelopes kept at ambient temperature.

Before being analyzed, hair is decontaminated, pulverized and then hydrolyzed using an acidic or alkaline solution. Buprenorphine and its metabolites, as well as illicit drugs are then extracted and analyzed, generally by means of a chromatographic technique coupled to mass spectrometry (18-20).

Almost all drugs of abuse and psychotropic drugs can be detected in hair. Segmental hair analysis provides an insight in the history of drug abuse, as well as (theoretically) of abstinence of a given individual. For that, the hair lock should be cut in 1 cm long segments, roughly corresponding to one-month growth (and exposure). Hair analysis cannot be used to adjust BU dose in patients, but it can be useful in determining the decrease in dose (or intake frequency) over time, or a prolonged period without administration (each individual being his or her own control). However, as for urine or plasma analyses, it does not seem to be able to detect irregular dosing. It is worth mentioning that, at least in France, there seems to be an important black market of buprenorphine sublingual tablets that have partly replaced street heroin. This market is mainly supplied by BU-maintained patients who do not take all their pills and above all try - and often succeed - to obtain several concomitant prescriptions from different general practitioners, as there is a very loose regulation of BU prescriptions.

However, hair analysis is of value in the monitoring of the efficiency of BU substitution treatments. As mentioned above, owing to the detection time-windows of DOA in urine, 2 or 3 urine screens would be necessary each week to document abstinence, which is costly, not withstanding the additional cost of confirmations (Table I).

Though hair analysis is more expensive, it can be performed much less often, e.g. every month at the beginning of the treatment and then every three months. Hair analysis provides semi-quantitative results (19,20), as shown in Figure 1 for a typical heroin addict treated by HD-BU : intensive heroin use (as shown by a high

concentration of 6-acetylmorphine, the primary and characteristic metabolite of heroin) is observed at the tip of the lock (about 6 months before sampling), then decreases in more recent segments when doses - and subsequently concentrations - of buprenorphine are increased. Thus, segmental hair analysis gives an estimate of the intensity (weak, medium or high) of an individual's drug use with respect to hundreds of such records, as well as of potential quantitative or qualitative changes in drug abuse, which may be useful to help the physician adjust the buprenorphine dose. The history recording property of hair is also particularly useful in situations where patients questioning is difficult or impossible (non-cooperating or psychiatric patients).

Finally, it is also sometimes useful or necessary for ex-drug addict to prove total abstinence from drugs of abuse to an employer or to the justice system. In this aim, on the personal request of the patient, analyses of 3 or 6 cm-long hair segments (or more) corresponding to the claimed period of abstinence can be performed.

Conclusions

The therapeutic drug monitoring of BU for dose adjustment was found to be deceiving, whatever the biological matrix analyzed (plasma, urine, hair), owing to the pharmacokinetic and pharmacodynamic properties of this drug. On the contrary, the monitoring of treatment compliance and efficacy (in terms of abstinence from other opiates) can be performed by means of either frequent urine screens for both buprenorphine and drugs of abuse or occasional, retrospective hair analyses. Hair analysis is therefore more informative and reliable than urine analysis but it is technically more demanding, hence both strategies can be regarded as complementary.

Table I : Main characteristics and performance of buprenorphine and drugs of abuse analyses in urine and hair.

	Urine	Hair
Drugs of abuse detected	All	All
Main compounds	Metabolites	Parent drugs
Detection time-window	2-3 days	Months, years
Analytical techniques	Immunoassays, followed by chromatography/mass spectrometry	Chromatography/mass spectrometry
Specificity	Family diagnosis, then specific identification	Specific identification
Analysis duration	+	+++
Type of measurement	incremental	cumulative
Sample collection	+/- invasive	non invasive
Adulteration	possible	Very difficult
Preservation	- 20° C	Ambient temperature

Figure 1 : Segmental analysis (cm by cm), over a period of 6 months, of a hair sample from a patient under buprenorphine substitutive treatment. The presence and concentration of 6-acetylmorphine are proofs of heroin abuse.

Références

1. Cowan A, Lewis J.W., Macfarlane I.R. Agonist and antagonist properties of buprenorphine, a new antinociceptive agent. *Br. J. Pharmacol.* 1977 ; 60 : 537-45.
2. Marquet P. Pharmacology of high-dose buprenorphine. In : Kintz P. & Marquet P. Buprenorphine therapy of opiate addiction, Ed. Humana Press, Totowa, NJ, USA, 1-12, 2002.
3. Levy G. What are narrow therapeutic index drugs ? *Clin. Pharmacol. Therap.* 1998 ; 63 : 501-5.
4. Walsh S.L, Preston K.L., Stitzer M.L., Cone E.J., Bigelow G.E. Clinical pharmacology of buprenorphine : ceiling effects at high doses. *Clin. Pharmacol. Ther.* 1994 ; 55 : 569-80.
5. Kuhlman J.J., Lalani S., Magluilo J., Levine B., Darwin W.D., Johnson R.E., Cone E.J. Human pharmacokinetics of intravenous, sublingual and buccal buprenorphine. *J. Anal. Toxicol.* 1996 ; 20 : 369-78.
6. Chawarski M.C., Schottenfeld R.S., O'Connor P.G., Pakes J. Plasma concentrations of buprenorphine 24 to 72 hours after dosing. *Drug Alcohol Depend.* 1999 ; 55 : 157-63.
7. Nath R.P., Upton R.A., Evehart E.T., Cheung P., Shwonek P., Jones R.T., Mendelson J.E. Buprenorphine pharmacokinetics : relative bioavailability of sublingual tablet and liquid formulations. *J. Clin. Pharmacol.* 1999 ; 39(6) : 619-23.
8. Tracqui A., Kintz P., Ludes B. Buprenorphine-related deaths among drug addicts in France : a report on 20 fatalities. *J. Anal. Toxicol.* 1998 ; 22(6) : 430-4.
9. Kintz P. Deaths involving buprenorphine : a compendium of French cases. *Forensic Sci. Int.* 200 ; 121(1-2) : 65-9.
10. Kintz P. A new series of 13 buprenorphine-related deaths. *Clin. Biochem.* 2002 ; 35(7) : 513-6.
11. Gaulier J.M., Marquet P., Lacassie E., Dupuy J.L., Lachâtre G. Fatal intoxication following self-administration of a massive dose of buprenorphine. *J Forensic Sci.* 2000 ; 45(1) : 226-8.
12. Kintz P. Buprenorphine : quelle méthode de dosage utiliser ? *Toxicorama* 1994 ; 6(3) : 19-29.
13. Hoja H., Marquet P., Verneuil B., Lotfi H., Dupuy J.L., Lachâtre G. Determination of buprenorphine and norbuprenorphine in whole blood by liquid chromatography-mass spectrometry. *J. Anal. Toxicol.* 1997 ; 21 : 160-5.
14. Moody D.E., Laycock J.D., Spanbauer A.C., Crouch D.J., Foltz R.L., Josephs J.L., Amass L., Bickel W.K. Determination of buprenorphine in human plasma by gas chromatography-positive ion chemical ionization mass spectrometry and liquid chromatography-tandem mass spectrometry. *J. Anal. Toxicol.* 1997 ; 21 : 406-13.
15. Tracqui A. Le poil : structure et physiologie. *Rev. Fr. Lab.* 1996 ; 282 : 19-23.
16. Cirimele V. Incorporation des xénobiotiques dans les cheveux. *Rev. Fr. Lab.* 1996 ; 282 : 31-5.
17. Tracqui A., Kintz P., Mangin P. HPLC/MS determination of buprenorphine and norbuprenorphine in biological fluids and hair samples. *J. Forensic Sci.* 1997 ; 42 : 111-4.
18. Wilkins D.G., Rollins D.E., Valdez A.S., Mizuno A., Krueger G.G. A retrospective study of buprenorphine and norbuprenorphine in human hair after multiple doses. *J. Anal. Toxicol.* 1999 ; 23 : 409-15.
19. Du Pont R.L., Baumgartner W.A. Drug testing by urine and hair analysis : complementary features and scientific issues. *Forensic Sci. In.* 1995 ; 70 : 63-76.
20. Kintz P. Drug testing in addicts : a comparison between urine, sweat and hair. *Ther. Drug Monit.* 1996 ; 18 : 450-5.