Serum concentration measurements of addictive drugs

Opioids, benzodiazepines and Z drugs are important and widely used drugs, but are associated with a risk of misuse, abuse and adverse effects. In some situations, serum concentration measurement may be useful to optimise treatment and detect misuse. In this article we show how such measurements can best be used, and present new reference ranges for these substances in serum, devised by the Norwegian Association of Clinical Pharmacology.

Addictive drugs such as opioids, benzodiazepines and Z drugs differ from other drugs in that they lead to development of tolerance and may lead to dependence and abuse. The substances have a significant level of toxicity and a risk of interacting with each other and with other central nervous system depressants such as alcohol. They also reduce cognitive and psychomotor skills and increase the risk of traffic accidents. Therefore, it is often appropriate for patients to use the lowest possible doses for the shortest possible period – and in many cases only as needed. However, the fact is that many patients use addictive drugs more or less permanently (1–3). In some patients, tolerance may develop over time, which leads to an increase in dosage. It is therefore difficult to define a therapeutic dose range, particularly for patients who need to use strong opioids over a longer period. Moreover, the dose requirement for opioids will vary considerably based on the type and degree of pain.

The use of serum concentration measurements to guide drug therapy is known as «therapeutic drug monitoring» (TDM). Serum concentration measurements may be considered useful when various clinical issues arise regarding the use of addictive drugs, such as therapeutic failure or adverse effects, unexpectedly strong or weak effect of a given dosage, or if overdose or toxicity is suspected. However, it is our experience that monitoring of adherence, i.e. whether patients keep to the prescribed dose, is the most frequent reason to order serum measurements of addictive drugs. For such measurements to have relevance, the serum concentration measured must necessarily be related to and interpreted in the light of a reference range.

«Many patients use addictive drugs more or less permanently»

Reference ranges for drugs

There is no unanimously accepted definition for the term «reference range» in TDM. For some drugs, the reference range will reflect the range of concentrations which most often provide a favourable relationship between efficacy and adverse effects. In these cases, the reference range is referred to as a therapeutic range. Well-known examples are aminoglycosides, methotrexate and digoxin.

Serum concentration measurements are also used for a number of drugs for which no defined therapeutic ranges are available, but for which we lack immediate clinical measurements of therapeutic effect. Examples of these are many antidepressants and antipsychotics, in addition to some newer antiepileptic drugs. For these types of drugs, the reference range is defined on a pharmacokinetic basis and reflects the range of concentrations that is normally achieved with the use of therapeutic doses (4). The reference range is then calculated based on a large number of measurements in a patient population, where the lower and upper limits for example correspond to the 10th and 90th percentiles of serum concentrations when therapeutic doses are used.

Although it has long been possible to measure the serum concentration of opioids, benzodiazepines and Z drugs, no well-defined reference ranges for these substances have previously existed. Published compilations of reference ranges are frequently dis-

Table 1 New upper reference limits for opioids. Upper reference limit corresponds to expected upper trough (pre-dose) concentrations using daily doses corresponding to 100 mg oral morphine equivalents (strong opioids), or highest daily dosage in the summary of product characteristics (weak opioids). The aim should be for the lowest effective dose.

Drug	Upper reference limit	Daily dose as basis for upper reference limit
Morphine	34 ng/ml (120 nmol/l)	100 mg
Oxycodone	63 ng/ml (200 nmol/l)	60 mg
Buprenorphine	1.2 ng/ml (2,5 nmol/l)[1] Opioid substition: 0.9–4.7 ng/ml (2–10 nmol/l)	2 mg (Higher doses for opioid substitution)
Fentanyl	3.4 ng/ml (10 nmol/l)[2]	1.2 mg (50 μg/h)
Ketobemidone	74 ng/ml (300 nmol/l)	100 mg
Pethidine	700 ng/ml (2 800 nmol/l)	1 000 mg
Codeine	250 ng/ml (850 nmol/l)	240 mg
Tramadol O-desmethyltramadol (active metabolite)	790 ng/ml (3 000 nmol/l) 100 ng/ml (400 nmol/l)[3]	400 mg

[1] Applies to sublingual administration. Low-dose transdermal buprenorphine seldom results in measurable serum concentrations with the methods of analysis used.
[2] Applies to transdermal use.
[3] O-desmethyltramadol is an active metabolite of tramadol, and presumably mediates the main component of the opioid effect.

Table 2 New upper reference limits for benzodiazepines and Z drugs. Upper reference limit corresponds to expected upper trough (pre-dose) concentrations, using the highest recommended daily dosage for anxiety/restlessness and/or insomnia. The aim should be for the lowest possible dose and short-term/intermittent use

Drug	Upper reference limit	Daily dose as basis for upper reference limit
Diazepam (incl. N-desmethyldiazepam)	1 000 ng/ml (3 500 nmol/l)[1]	15 mg
Oxazepam	720 ng/ml (2 500 nmol/l)	45 mg
Alprazolam	50 ng/ml (160 nmol/l)	3 mg
Clonazepam	16 ng/ml (50 nmol/l) Epilepsy: 20–70 ng/ml (60–220 nmol/l)	1.5 mg (Higher doses for epilepsy)
Nitrazepam	84 ng/ml (300 nmol/l)[2]	5 mg
Flunitrazepam	6 ng/ml (20 nmol/l)[2]	1 mg
Zopiclone	20 ng/ml (50 nmol/l)[2]	7,5 mg (5 mg in the elderly)
Zolpidem	30 ng/ml (100 nmol/l)[2]	10 mg (5 mg in the elderly)

[1] Diazepam converts to the active metabolite N-desmethyldiazepam, which is also quantified. Upper reference limit applies to the sum of diazepam plus N-desmethyldiazepam.

[2] Upper reference limit for Z drugs and benzodiazepines for insomnia applies to samples taken a minimum of 12 hours after intake.

cordant, and often little information is available with regard to the basis for the reference ranges, and how test results should be interpreted in light of these (4, 5). As a result, the pharmacological laboratories have lacked a solid basis on which to interpret serum concentration measurements and provide guidance for the requisitioning doctors, and different laboratories have specified different reference limits for these substances.

New reference ranges

In 2014, the Norwegian Association of Clinical Pharmacology established a working group to prepare common reference ranges for opioids, benzodiazepines and Z drugs. The launch of the Pharmacology Portal (6), a national web portal for pharmacological and toxicological analyses in Norway, made this work all the more necessary and the working group recently submitted its conclusion (Table 1 and Table 2) (7).

Since the therapeutic effect will largely depend on the patient's primary condition and the individual degree of tolerance, it is difficult to define therapeutic ranges for these drugs. Instead, the working group considered that upper reference limits should reflect the expected upper trough (pre-dose) concentrations, using the highest daily dosage for the main indications for these groups of substances – treatment of pain for opioids, and of anxiety and insomnia for benzodiazepines and Z drugs, respectively. Lower reference limits were not considered appropriate, as the serum concentration for these drugs should generally be kept as low as possible. The highest daily dosage of weak opioids, Z drugs and benzodiazepines was defined on the basis of the recommended doses given in Norwegian or Swedish summaries of product characteristics (SPCs). There is no well-defined maximum dose for strong opioids. We chose equianalgesic doses corresponding to 100 mg oral morphine daily (8) as a basis for calculating upper reference limits for strong opioids, since the great majority of those using opioids over a longer period will use lower doses (1). The doses are rounded to the nearest practical daily dosage for marketed drug formulations. The calculation of upper reference limits from the defined upper daily dosages is based on a review of published pharmacokinetic studies and the laboratories' own TDM databases.

BOX 1

Indications for serum concentration measurement of addictive drugs

- Monitoring of drug adherence
- Therapeutic failure at standard dosage
- Unexpected or pronounced adverse effects at standard dosage
- Suspected overdose or symptoms of intoxication
- Diagnosis of misuse/abuse (urine samples usually more suitable)

Recommendations for use

With the new reference limits that have been established, the laboratories are better equipped to interpret serum concentration measurements of addictive drugs. In the great majority of cases, patients who keep within the recommended dose range will have trough serum concentrations lower than the reference limit. Concentrations above the reference limit may indicate use of higher doses than recommended, having excluded the possibility of inappropriate sampling time. There is nevertheless a significant variation from patient to patient, and many factors may affect the relationship between serum concentration and dosage. Impaired organ function or age-related pharmacokinetic changes may increase the serum concentration, while drug interactions and genetically determined deviations in drug metabolism may yield higher or lower serum concentration than expected.

When ordering serum concentration measurements, doctors should ensure that the samples as far as possible are taken at trough level, in other words, immediately before the next dose. Samples taken close to peak concentration will be misleading and cannot be compared to the reference limits. Information on dosage, time of last intake and time of sampling must be provided for the laboratory to be able to give an interpretation of the test result, including whether the measured serum concentration is consistent with the given dosage. We recommend contacting the laboratory in question in case of doubt as to how the serum concentration measurements should be interpreted, and preferably in advance of the sample being taken if there is any question regarding the procedure.

Arne Helland
arne.helland@stolav.no
Jon Andsnes Berg
Ingebjørg Gustavsen
Kristin Nordal
Thor Hilberg
Lena Aronsen
Marianne Arnestad
Sigrid Narum

Arne Helland (born 1977), specialist in clinical pharmacology and head of section/senior consultant at the Department of Clinical Pharmacology, St. Olavs Hospital (Trondheim University Hospital).

The author has completed the ICMJE form and reports no conflicts of interest.

>>>

Jon Andsnes Berg (born 1978), specialist in clinical pharmacology and acting senior consultant at the Section of Clinical Pharmacology, Laboratory of Clinical Biochemistry, Haukeland University Hospital.
The author has completed the ICMJE form and reports no conflicts of interest.

Ingebjørg Gustavsen (born 1972), specialist in clinical pharmacology and head of section/senior consultant at the Ullevål branch of the Department of Pharmacology, Oslo University Hospital.
The author has completed the ICMJE form and reports no conflicts of interest.

Kristin Nordal (born 1976), specialist in clinical pharmacology and doctor at the Department of Pharmacology, Oslo University Hospital.
The author has completed the ICMJE form and reports no conflicts of interest.

Thor Hilberg (born 1957), specialist in clinical pharmacology and senior consultant at Fürst medical laboratory, Oslo.
The author has completed the ICMJE form and reports no conflicts of interest.

Lena Aronsen (born 1971), specialist in clinical pharmacology and senior consultant at the Department of Laboratory Medicine, University Hospital of North Norway.
The author has completed the ICMJE form and reports no conflicts of interest.

Marianne Arnestad (born 1970) was a specialty registrar in clinical pharmacology at the Centre for Psychopharmacology, Diakonhjemmet Hospital in connection with the preparation of the report on which this article is based. She is now a senior consultant at the Domain for Forensic Sciences, Norwegian Institute of Public Health, and a board member of the Norwegian Association of Clinical Pharmacology.
The author has completed the ICMJE form and reports no conflicts of interest.

Sigrid Narum (born 1969), specialist in clinical pharmacology and head of section/senior consultant at the Centre for Psychopharmacology, Diakonhjemmet Hospital and chair of the specialist committee in clinical pharmacology.
The author has completed the ICMJE form and reports no conflicts of interest.

All the authors work in laboratory departments offering drug analyses. None of the authors derives any direct personal financial gain from the analyses.

References

1. Nasjonal faglig veileder bruk av opioider – ved langvarige ikke-kreftrelaterte smerter. Oslo: Helsedirektoratet 2015. https://helsedirektoratet.no/retningslinjer/opioider (10.6. 2015).
2. Nasjonal faglig veileder vanedannende legemidler – rekvirering og forsvarlighet. Oslo: Helsedirektoratet 2015. https://helsedirektoratet.no/retningslinjer/vanedannende-legemidler (28.12.2015).
3. Skurtveit S, Sakshaug S, Hjellvik V et al. Bruk av vanedannende legemidler i Norge 2005–2013. Oslo: Folkehelseinstituttet, 2014.
4. Hiemke C, Baumann P, Bergemann N et al. AGNP consensus guidelines for therapeutic drug monitoring in psychiatry: update 2011. Pharmacopsychiatry 2011; 44: 195–235.
5. Schulz M, Iwersen-Bergmann S, Andresen H et al. Therapeutic and toxic blood concentrations of nearly 1,000 drugs and other xenobiotics. Crit Care 2012; 16: R136.
6. Bjånes TK, Westin AA. Nettportal for legemiddelanalyser. Tidsskr Nor Legeforen 2015; 135: 635–6.
7. Serumkonsentrasjonsmålinger av vanedannende legemidler. Farmakologiportalen. http://farmakologiportalen.no/nasjonale_referanseomrader (3.2.2016).
8. Svendsen K, Borchgrevink P, Fredheim O et al. Choosing the unit of measurement counts: the use of oral morphine equivalents in studies of opioid consumption is a useful addition to defined daily doses. Palliat Med 2011; 25: 725–32.

Received 11 January 2016 and accepted 8 February 2016. Editor: Ketil Slagstad.