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Lower reporting limit for detection of cocaine

PERSPECTIVES

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Consumption of cocaine in Norway is amongst the highest in Europe, and the number of positive urine tests is on the increase. A lower national reporting limit for cocaine can lead to more straightforward cooperation between laboratories and a greater number of positive tests.

In recent years, seizures of cocaine in Norway have increased, and consumption is amongst the highest in Europe (1). Meanwhile, the degree of purity of the drug is significantly higher than before, which may indicate both increased consumption and higher doses (2). On occasion, a specimen donor challenges an analysis result. Consequently, Norwegian laboratories should agree on the same reporting limits.

The detection window depends on the pattern of use

How long cocaine and its metabolite benzoylecgonine (BZE) can be detected in urine following the most recent intake of cocaine (the detection window) depends on the reporting limits of the individual laboratory as well as whether the drug was administered as a single dose or used repeatedly over time (3–5).

Cocaine is a lipophilic substance that is distributed to several body tissues. When large amounts of cocaine are consumed over time, the substance accumulates in the central nervous system, for example, and then slowly enters the bloodstream (6). Even when the levels are too low to be detected in blood samples, the substance can often be traced in urine. Cocaine is metabolised very quickly after intake, including into the inactive metabolite BZE. Both cocaine and BZE are excreted in urine. Normally BZE is found in higher concentrations than cocaine and has a longer detection window. As a result, this metabolite is used as a marker for cocaine intake, alone or in combination with cocaine (7).

It is usually reported that cocaine can be detected in urine up to 4–5 days after intake. Up until now, there has been little awareness in Norway of the fact that the detection window largely depends on the pattern of cocaine use. When there is a high reporting limit, the detection window of 4–5 days can be attributed to a single intake of an ordinary drug dose (3). Studies of chronic cocaine users have shown that detection time in the urine after intake of repeated cocaine doses over time can be up to three weeks (reporting limits 1–300 ng/ml) (4, 5, 8).

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In the first phase after intake, the half-lives for cocaine and BZE will be short, in the order of hours, while in the final phase of BZE elimination in urine, a long half-life of several days is observed (5). This is typical of biphasic elimination, and these low concentrations, which can be detected for a considerable period of time, are often referred to as a 'tail' (3, 8) (Figure 1). A similar long detection time after long-term, high intake is also seen in the case of cannabis (8).

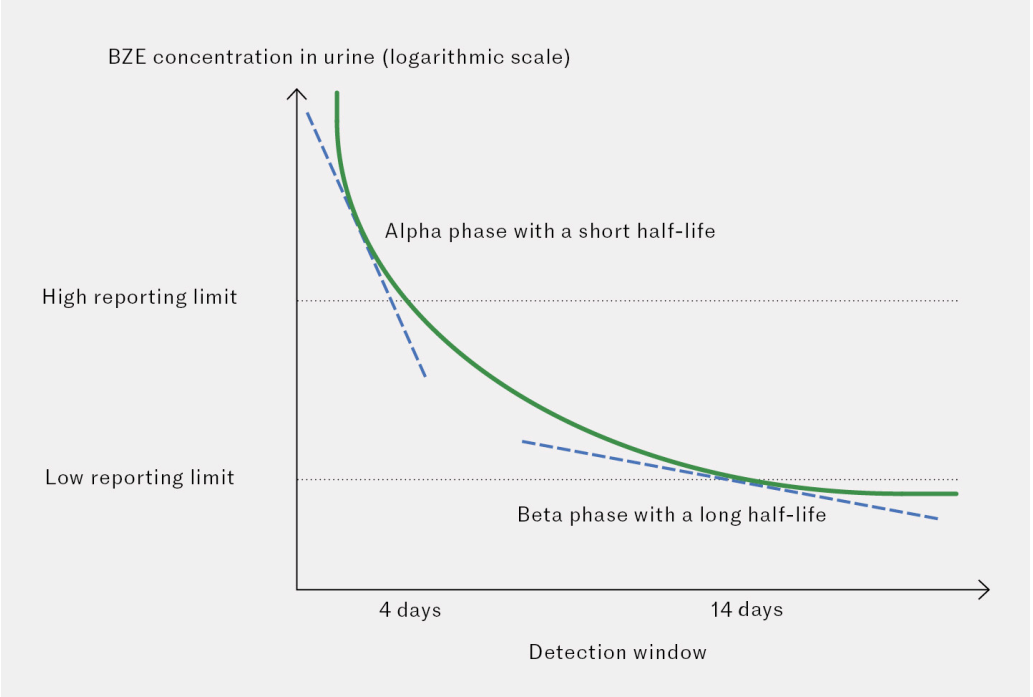

Figure 1 Example of biphasic elimination of BZE after repeated cocaine intake. First we see an alpha phase with a short half-life followed by a beta phase with a longer half-life. A low reporting limit would give a significantly longer detection window compared with a high reporting limit.

Lower reporting limit

The detection window after intake of an illegal drug will not only depend on how much has been taken, but also on what reporting limit the laboratory uses. The reporting limit is the lowest concentration which the laboratory reports as 'detected' or as a positive result. This means that small amounts of the substance can be found in the sample, even though the result is given as 'negative' or 'not detected'. Consequently, the laboratories' choice of reporting limits is important in relation to the detection time.

A high reporting limit for BZE may entail that the concentrations forming the 'tail' are not detected, i.e. the lowest concentrations. When the reporting limit is low, even small amounts can be detected, leading to a longer detection window (Figure 1).

Low reporting limits can result in analytical challenges as other substances present in the specimen may interfere with the analysis. This may mean that the specimens must be analysed several times in order to ensure the correct analysis, which prolongs the time taken to give the result and increases the use of resources.

Reporting limits of up to 100 ng/ml for specific (chromatographic) analysis of BZE in urine have been used (9). Thus a large number of specimens will be assessed as negative even though they actually contain low concentrations of cocaine and/or BZE. A 2016 US study examined approximately 4 200 urine specimens where BZE was detected in the urine at a reporting limit of 5 ng/ml. Their data show that if a reporting limit of 100 ng/ml had been used, around

half of the specimens would have been reported as negative (5). Figures from Haukeland University Hospital reveal that most specimens with findings of BZE show low concentrations (Figure 2).

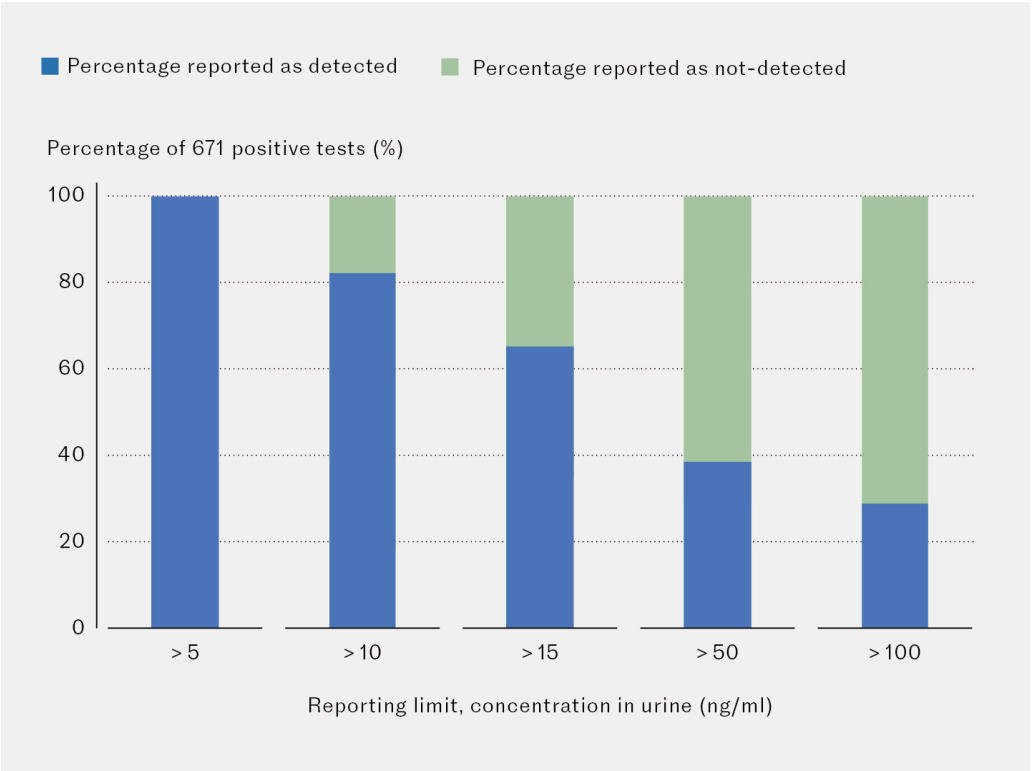

Figure 2 Percentage of positive specimens distributed by different reporting limits out of a total of 671 positive urine specimens. Figures from the Section of Clinical Pharmacology, Haukeland University Hospital.

Harmonisation of reporting limits

Several factors should be taken into account in determining how low the reporting limit should be. Laboratories have previously chosen a reporting limit they considered appropriate. This means that laboratories have different limits. The reporting limits for BZE using specific analysis vary from 15 ng/ml to 100 ng/ml at different laboratories in Norway (9).

> ***«Laboratories have previously chosen a reporting limit they considered appropriate. This means that laboratories have different limits»***

In addition, some laboratories perform immunological screening prior to confirming an analysis. Immunological analyses are easier to conduct, and negative results can be reported quickly. But such screening analyses are non-specific and often have a higher reporting limit and thus a risk of false positives in the case of cross-reactions as well as negative results in tests where BZE concentrations are low.

Different reporting limits are problematic in situations where the specimen donor challenges a test result, and the specimen is analysed at another laboratory for a second opinion. The consequence may be that a test result at

one laboratory might be 'positive'/'detected', and at another 'negative'/'not detected'. Such differences may create uncertainty regarding the results, and result in unequal treatment and consequences for the sample donor in different parts of the country.

The need to harmonise reporting limits is heightened by the decision that the results of illegal drug analyses in the future will be transferred to the summary care record and *Helsenorge*. This will be presented in a general overview for health personnel and patients (10).

Cocaine does not need to be analysed

In spring 2024, a national working group was appointed by the Norwegian Association of Clinical Pharmacology to investigate the need for a national harmonisation of reporting limits for cocaine and BZE in urine. The working group consisted of senior consultants and specialty registrars in clinical pharmacology with experience with analyses of illegal drugs from nine laboratories. All the laboratories offer specific analysis of cocaine and/or BZE in urine.

> ***«The working group recommended that reporting limits for medical tests should be harmonised, setting the appropriate limit at 15 ng/ml»***

The working group recommended that reporting limits for medical tests should be harmonised, setting the appropriate limit at 15 ng/ml. They also discussed whether cocaine should be analysed in addition to BZE but found no basis for such a recommendation. The recommended reporting limit is within the lower level of limits applied by the laboratories prior to the harmonisation work. Several laboratories will thus lower their limits as a result of this recommendation.

At this stage, the working group has only suggested a limit for medical tests, not for analyses in samples where the results can lead to sanctions. The result of the latter type of testing may, on its own, lead to serious sanctions in, for example, the correctional service, child welfare and working life. This type of testing may require a different reporting limit and greater margins of safety.

The risk of misinterpretation

With a lower reporting limit, it is important that care be taken when interpreting test results, considering that the detection window is longer than previously. For example, with a lower limit, a 'positive' urine specimen taken two weeks after the most recent intake does not necessarily mean new intake of cocaine, but may be a result of high consumption in the time prior to the most recent intake. This can also be observed at a higher limit but will be seen more frequently with a lower limit.

The laboratories can assist the requisitioner and other health personnel by comparing results from several tests over time in order to help interpret positive test results. Requisitioners are recommended to contact the laboratory to discuss marginal cases, whether this concerns a new intake or not.

Harmonisation for other illegal drugs

Harmonisation of analysis methods and reporting limits for illegal drugs can result in uniform and predictable patient follow-up nationally, and simplify cooperation between laboratories. The working group believes that there is also a need for harmonisation of the interpretation of test results and reporting limits for other illegal drugs, as is the case in Sweden (11).

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