

Pharmacological indicators of road safety related impairments in the acute and post-acute cocaine phase

Anja Knoche¹

The current political discussion in Germany mainly concerns the assessment of drug users' driver fitness. The key committee, responsible for the standardisation of the respective assessment procedures, *inter alia* deals with the determination of analytical limit values for different types of drugs. As a member of this committee we had the task to clarify whether and to which extent the cocaine metabolite Benzoyllecgonine (BZE) can be used as an indicator for road safety related impairments of cocaine users.

Cocaine abuse is usually inferred by the detection of cocaine or the cocaine metabolite benzoyllecgonine (BZE) in the urine, blood or hair. In order to assess the degree of behavioural impairments resulting from cocaine consumption that may have effects on real life problems, such as road safety, it is necessary to establish a relationship between the amount of consumed cocaine, the resulting time course of cocaine or BZE in the urine, blood or hair, and the time course of possible neuropsychological deficits. An important question is if there are still behavioural deficits beyond the time when no cocaine can be detected in the body.

Pattern of consumption

Cocaine users are either occasional users or cocaine addicts. Occasional users are usually able to control their cocaine consumption and to abandon cocaine intake. They consume small amounts usually intranasal (i.n.) with intervals of days to weeks. There are only mild withdrawal symptoms reported. Normally, occasional users do not belong to disadvantaged groups. Only a relatively small percentage of 10-15% of the i.n. initial users develops later cocaine addiction [12]. The risk of developing a cocaine addiction is increased in persons with premorbid personality disturbances, like anxiety or depression [23], and in persons with certain personality traits like high novelty seeking, high risk seeking, low decision making and low cognitive abilities [1]. The transition from occasional user to a cocaine addict usually takes 2-4 years. During that time the amount of consumed cocaine increases. The way of application changes from intranasal to intravenous intake or crack cocaine smoking [12]. Binge taking is the characteristic pattern of cocaine intake in addicts. During a binge euphoria is experienced, and other natural reinforcers lose importance, as thinking is fixed only on cocaine. Acute tolerance develops for the euphoric and the physiological effects during a cocaine

binge. The dose of self-administered cocaine increases during the binge. A binge usually lasts 4-24 hours and it consists of cocaine self-administrations in intervals of 10-30 min until cocaine is no longer available any more. In cocaine addicts 1-7 binges are reported per week [12].

Neuropsychological assessments of the cocaine effects on behaviour

Occasional cocaine users

Neuropsychological experiments with occasional users usually focus on a time frame within the first 4 hours after cocaine intake, i.e. a time at which cocaine and BZE are both detectable in the plasma or urine. Studies in a laboratory setting showed that cocaine did not impair visual attention, reaction time, learning and memory [15, 27]. Cocaine improved sleep-deprivation-induced attention deficits in a signal detection task [9]. Although Stillman and colleagues [27] reported reduced fatigue and increased attention scores 4 hours after cocaine intake, there are also reports for the subjective experience of sedation and a decrease of euphoria 4-8 hours after cocaine intake [9]. Interestingly, there is evidence for an increased aggression level in occasional users after cocaine intake [18]. Altogether, neuropsychological assessments of the cocaine effects on behavior in occasional users did not show neuropsychological or emotional deficits in the acute phase until 4 hours after cocaine intake. With increased attention and shortened reaction times they rather indicate an improvement in some neuropsychological measures after cocaine in occasional users. It is unclear if the increased aggression level after cocaine in the acute phase is of any relevance for behavioural tasks in real live situations. Unfortunately, there are no studies with occasional users that investigate the effects of cocaine in the post-acute phase, i.e. starting 4 hours after intake. At the present stage a rebound effect, that may consist of lowered attention and prolonged reaction times, can not be ruled out in the post-acute phase. It should be emphasized that the clinical studies on cocaine employed low to medium doses of cocaine. Therefore, from the present data one can not make conclusions regarding possible impairments after high or very high doses, that may be "accidentally" consumed by occasional users. At the present stage, however, there is no evidence for neuropsychological impairments in the acute cocaine phase in occasional users. Accordingly, a measured cocaine or BZE concentration in the plasma, urine, or hair of a occasional user may be considered as an indicator of cocaine consumption, but not necessarily as an indicator of behavioural impairments. The case is different with people who are known cocaine addicts.

Cocaine addicts

In general, it is important to differentiate between a cocaine addict who is abstinent and one who consumed cocaine within the last days. It was shown that cocaine addiction itself, without acute

cocaine intake, is associated with a number of neurological and neuropsychological impairments. There is evidence for brain perfusion deficits and cerebral atrophies in cocaine addicts [19] which can persist several weeks after withdrawal. The energetic status of the brain, i.e. the metabolism of high energy phosphates and phospholipids, is attenuated [7]. The glucose metabolism of the brain can be lower until 3-4 month of withdrawal. The EEG of cocaine addicts is diffusely slowed down [22], while the activity of the HPA-axis, which is responsible for the stress state of the body, is chronically enhanced [17]. Cocaine addicts may show a resting tremor with a frequency of 4-6 Hz, but have a normal action tremor. The resting tremor is probably not relevant for daily life but may affect fast or exact movement, as they are required for, e.g., driving a car [4]. Cocaine addiction may also induce psychiatric diseases like depression and schizophrenia, or may aggravate existing depressive symptoms [30]. There is also a wide range of neuropsychological impairments reported in abstinent cocaine addicts. Beatty and colleagues [5] reported task specific deficits in learning and memory. Several studies showed that declarative memory (remembering a complex geometric figure), auditory and visual short term memory were impaired, while procedural memory (remembering a movement) and visuospatial memory were improved [3, 14, 20, 29]. In general, verbal memory was unaffected in cocaine addicts [20, 29]. Cocaine addicts also showed impairments in arithmetic tests, in problem solving and abstraction [3, 16, 21, 26]. There were no indications of impaired sustained attention or vigilance [4, 5]. However, Roberts and Bauer [24] found deficits in divided visual and auditory attention.

Taken together, there is a broad spectrum of neurological and neuropsychological impairments in cocaine addicts during withdrawal that persist at least 3-4 month. The clinical diagnosis of cocaine addiction would, thus, by itself already imply deficits in complex behavioural tasks for a time of at least 3-4 month of abstinence. As such, the determination of cocaine or BZE in the hair would not be necessary as an additional pharmacological indicator. Currently, it is unclear if the neuropsychological and neurological deficits in cocaine addicts persist longer than 4 month. Further investigations are necessary that address this question.

If a known cocaine addict consumes cocaine the existing deficits add up to the acute cocaine effects, which are different from the effects in occasional users. Cocaine addicts consume cocaine in a binge pattern. A binge is usually followed by 1.) a crash, 2.) a withdrawal period and 3.) an extinction period [10, 12]. The crash sets in 15-30 min after the last cocaine dose of the binge, and can last between 9 hours and 4 days. It starts with a depression, anhedonia, insomnia, irritability, and anxiety. People feel confused and fatigued. Some cocaine addicts also report suicidal tendencies and paranoia in the beginning of the crash. At very high doses of consumed cocaine a so called cocaine-psychosis can occur. The symptoms of a cocaine-psychosis are hard to differentiate from that of a paranoid schizophrenia: complex paranoid delusions, hallucinations and bizarre behavior. However, affect is preserved and there are no formal thinking disturbances [11, 25]. A prominent

symptom of a cocaine-psychosis are the so called "cocaine bugs": the tactile hallucination and delusion of insects underneath the skin and in the environment. Even if no cocaine-psychosis is developed, delusions and suspiciousness for internal and external perception can occur [8]. During the crash dysphoric arousal changes to dysphoric lethargy and a loss of energy. This is followed by fatigue, hypersomnolence, and hyperphagia. As such, the crash constitutes a phase of heavy emotional and behavioural disturbances. To our knowledge, there are no neuropsychological data available about the early crash phase. In the late crash phase (72 hours after the end of the binge) neuropsychological deficits are comparable to those of the abstinence period: memory impairments, impaired visuospatial abilities and concentration deficits [6]. The crash is succeeded by the withdrawal period with normal affective functions, but the development of cocaine craving. This can last from 1 to 10 weeks. During the withdrawal period fluctuating clinical syndromes develop that consist of anhedonia, dysphoria, anxiety, irritability and a general loss of energy. Craving starts to develop, which may cause a relapse to binge taking of cocaine [10, 12]. If no relapse occurs, an extinction period follows with an unlimited duration. During the extinction period neuropsychological impairments are these of a cocaine addict during abstinence. If cocaine addiction is known for a person, and in addition to that, cocaine is detected at any concentration in the plasma or urine, it is likely that a binge occurred no longer than 12-24 hours ago. This suggests that the respective person is experiencing a crash, which is associated with heavy emotional, motivational, and behavioural disturbances. In this stage, no task that requires concentration, perception, cognition, or decision making abilities should be executed. If BZE, but no cocaine is detected in the urine of a known addict, the binge occurred no longer than 10-22 days ago. This suggests that the respective person is either in the late crash or in the extinction period. Both are associated with emotional disturbances that add up to the neuropsychological and neurological impairments of cocaine addiction in general. Also in this case impairments in complex behavioural tasks, like driving a car, are very likely.

At the present stage, cocaine addiction has to be clinically diagnosed. Although cocaine and BZE can be detected in the hair, it is difficult to distinguish occasional users from addicts by the concentration of cocaine or BZE in the hair due to a high interindividual variance in the incorporation of both substances into the hair. Unfortunately, a sole qualitative detection of cocaine or BZE in the hair is not sufficient as criterion, since also occasional users show detectable amounts of cocaine in the hair. In order to use the concentration of cocaine or BZE in the hair as a criterion, a quantitative detection will be necessary [28]. To our knowledge, however, thresholds for cocaine or BZE in the hair that separate occasional users from cocaine addicts have not yet been established.

Detection of Cocaine and BZE

Cocaine can be detected in the urine shortly after consumption and until 8-12 hours afterwards. BZE, however, can be detected until 60 hours after consumption [13], and in cases of severe addiction even until 10-22 days afterwards [31]. Several lines of evidence indicate strong interindividual, gender- and race-specific differences in the metabolism of cocaine, and, thus, in the amount of BZE that is formed after the consumption of a certain amount of cocaine [32]. There appears a general amount-latency problem, which suggests that from a measured amount of BZE it will be very difficult to infer both, the amount of consumed cocaine and the latency of intake [2]. A certain amount of BZE detected in the plasma or urine can result either from a high dose of cocaine with a long latency or a low dose of cocaine with a shorter latency of intake. In reality, the formation of BZE is further confounded by the intake of adulterating substances or other drugs, such as alcohol, that may interact with cocaine metabolism and with the behavioural effects of the cocaine.

Conclusions

In conclusion, there is no evidence for neuropsychological or neurological impairments after cocaine consumption in occasional users at low to medium doses of cocaine. As such, a measured BZE or cocaine concentration in the plasma, urine, or hair may not be considered to be a useful indicator of behavioural impairments. If cocaine addiction is clinically diagnosed in a person, at least until 3-4 month of abstinence a great number of neuropsychological impairments is evident that suggest deficits in complex behavioural tasks. If BZE or cocaine is detected in the plasma or urine of a known cocaine addict, it becomes very likely that the last cocaine intake was not long ago. At this stage, in addition to the addiction-induced neuropsychological impairments, also significant emotional and motivational disturbances are manifested. Complex behavioural tasks, like driving a car, should be even more impaired than in abstinent cocaine addicts. However, it is not always known whether a person is a cocaine addict or an occasional user. Quantitative hair analysis may be a useful tool to differentiate both groups, however, further research is required in order to establish a threshold for objective differentiation.

The initial question, whether we can conclude the amount of consumed cocaine or the latency of intake from a certain BZE-concentration must be negated. Thus the BZE concentration alone is no indicator for the degree of behavioural impairment in traffic safety.

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Section Traffic Psychology, Traffic Medicine

Brüderstr. 53

51427 Bergisch-Gladbach

Germany

email: knoche@bast.de