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Acute poisoning from substance abuse of benzodiazepines

SHORT REPORT

JON ANDREAS ANDERSSON

Faculty of Medicine University of Oslo
and
Valnesfjord Medical Centre
Fauske Municipality
Jon Andreas Andersson is a general practitioner.
The author has completed the ICMJE form and declares no conflicts of interest.

METTE BREKKE

General Practice Research Unit
University of Oslo
Professor Mette Brekke is a specialist in general practice.
The author has completed the ICMJE form and declares no conflicts of interest.

ODD MARTIN VALLERSNES

E-mail: o.m.vallersnes@medisin.uio.no
Department of General Practice
University of Oslo
and
Department of Emergency General Practice
Oslo Accident and Emergency Outpatient Clinic
City of Oslo Health Agency
Odd Martin Vallersnes is associate professor and a consultant general practitioner.
The author has completed the ICMJE form and declares no conflicts of interest.

BACKGROUND

Benzodiazepines are also used as intoxicants. This can be dangerous, particularly in multi-substance abuse. We describe of acute poisoning related to substance abuse of benzodiazepines in patients at the main A&E clinic in Oslo.

MATERIAL AND METHOD

We included all patients treated for substance abuse poisoning with benzodiazepines and/or z-hypnotics at the Oslo Acc and Emergency Outpatient Clinic from 1 October 2013 to 30 September 2015. The patients were found through a retrosp review of the A&E clinic's registers. Data were taken from patient records. Diagnosis of the toxic agent was based on the attending doctor's recorded clinical evaluation.

RESULTS

Of 1 037 cases, 787 (76 %) were men. The median age was 36 (interquartile range 28–46, range 14–78). Clonazepam (Ri was the most frequently occurring drug, with 575 cases (55 %), followed by diazepam (Stesolid, Valium, Vival) 158 (15 % alprazolam (Xanor) 125 (12 %) and oxazepam (Sobril) 94 (9 %). Zopiclone (Imovane, Zopitin) and zolpidem (Stilnoct) o rarely, in 25 (2 %) and 11 (1 %) cases, respectively. Benzodiazepines were combined with other intoxicants in 936 (90 %) most frequently heroin 484 (47 %), ethanol 321 (31 %) and amphetamine 199 (19 %).

INTERPRETATION

In substance abuse poisoning, benzodiazepines were very often combined with other intoxicants, most frequently opioic ethanol and/or amphetamine.

Main findings

Clonazepam (Rivotril), diazepam (Stesolid, Valium, Vival) and alprazolam (Xanor) were the most commonly occurring benzodiazepines in substance abuse poisoning.

In nine out of ten cases, benzodiazepines had been taken in combination with other intoxicants.

The use of benzodiazepines has increased sharply since they were first synthesised in the 1950s, and they have gradually replaced barbiturates and other hypnotic and anti-anxiety drugs (1). In 2008, 6 % of the Norwegian population was pres at least one benzodiazepine (2). Since the 1990s, z-hypnotics such as zopiclone (Imovane, Zopitin) and zolpidem (Stilno have taken over for insomnia (3).

Benzodiazepines and z-hypnotics are chemically dissimilar, but both act by increasing the effect of the neurotransmitter gamma-aminobutyric acid (GABA) on $GABA_A$ receptors in the brain. This reduces neuronal excitability, with a hypnotic anxiolytic and anticonvulsive effect as a result (4, 5).

Benzodiazepines can also be used as intoxicants, and have adverse long-term effects in the form of impaired cognitive al and risk of dependence. Overdosing results in altered level of consciousness, impaired coordination, amnesia and respir depression. The risk of an overdose is greatest in combination with other intoxicants with depressant effects. Flumazeni antidote, but has a short half-life and may cause seizures (4, 5).

Z-hypnotics cause less intoxication and entail less risk of inducing dependence (5), but the mechanism is otherwise so si to benzodiazepines that we have chosen to include them in this study. In the following we use benzodiazepines as a colle term.

12 % of benzodiazepine users account for 59 % of prescribed use in Norway (6). A Swiss study found that heavy users oft alternate between legal and illegal strategies to acquire benzodiazepines (7). In an anonymous British questionnaire sur sources of benzodiazepines were general practitioners (55 %), friends and family (40 %), online purchasing (27 %), stree (20 %) and abroad (11 %). Multiple sources were used by 31 %.

We describe acute poisonings treated by the main A&E clinic in Oslo, due to substance abuse of benzodiazepines, with emphasis on the type of benzodiazepine and other intoxicants they were taken in combination with.

Material and method

We included all cases of substance abuse poisoning with benzodiazepines treated by the main A&E clinic in Oslo (the Os Accident and Emergency Outpatient Clinic (OAEOC)), and retrospectively reviewed cases registered by the reception nu the patient registration lists in the A&E clinic's electronic record system in the period October 2013–September 2015. Poisonings with suicidal intention were not included.

From patient records we noted age, sex, toxic agent, whether the patient was brought by ambulance, observation period treatment, disposition and a fixed set of symptoms and signs, in accordance with a data registration template developed research network European Drug Emergencies Network (Euro-DEN) (9). Diagnosis of the toxic agent was based on the attending doctor's assessment as noted in the records, which in turn was based on information from the patient and/or supplied by third parties, and on clinical findings. No toxicological laboratory diagnostic work was performed.

The project was carried out as a quality improvement study and was approved by the Information Security and Privacy C Oslo University Hospital.

SPSS version 25 was used to perform analyses. We used the chi-squared test to compare categorical variables.

Results

Benzodiazepines were involved in 1 037 substance abuse poisonings in the course of a two-year period. The median age patients was 36 years (interquartile range 28–46, range 14–78, and 787 (76 %) were men.

Clonazepam (Rivotril) occurred most frequently, with 575 (55 %) cases, followed by diazepam (Stesolid, Valium, Vival) 1 (15 %) and alprazolam (Xanor) 125 (12 %) (Table 1).

Table 1

Combinations of benzodiazepines (including z-hypnotics) and other intoxicants in acute poisoning cases treated at the main A&E cl Oslo from 1.10.2013–30.09.2015. Data are stated as number (%) The total number may be higher than the sums in columns or rows several benzodiazepines might be combined with the same intoxicant and several intoxicants could be combined with the same benzodiazepine. GHB = gamma hydroxybutyrate, MDMA = methylenedioxymethamphetamine

	Heroin	Methadone	Buprenorphine	Other opioids	Amphetamine	Cocaine	MDMA	GHB	Cannabis	Ethanol	Other / unknown	Only benzodiazepine
Clonazepam (Rivotril)	318 (66)	28 (62)	23 (68)	21 (29)	131 (66)	18 (56)	10 (56)	31 (63)	62 (65)	159 (50)	10 (43)	45 (45
Diazepam (Stesolid, Valium, Vival)	48 (10)	8 (18)	1 (3)	10 (14)	24 (12)	5 (16)	2 (11)	8 (16)	18 (19)	82 (26)	6 (26)	13 (13
Alprazolam (Xanor)	77 (16)	4 (9)	6 (18)	7 (10)	27 (14)	6 (19)	3 (17)	5 (10)	10 (11)	23 (7)	1 (4)	12 (12
Oxazepam (Sobril)	28 (6)	4 (9)	3 (9)	8 (11)	14 (7)	2 (6)	2 (11)	3 (6)	8 (8)	35 (11)	3 (13)	14 (14
Flunitrazepam (Rohypnol)	14 (3)	1 (2)	1 (3)	2 (3)	7 (4)	1 (3)	2 (11)	4 (8)	4 (4)	7 (2)	-	5 (5
Zopiclone (Imovane, Zopitin)	3 (1)	-	-	2 (3)	-	-	-	-	2 (2)	13 (4)	-	7 (7

	Heroin	Methadone	Buprenorphine	Other opioids	Amphetamine	Cocaine	MDMA	GHB	Cannabis	Ethanol	Other / unknown	Only benzodiazepine
Nitrazepam (Apodorm, Mogadon)	7 (1)	-	1 (3)	2 (3)	2 (1)	1 (3)	-	2 (4)	-	5 (2)	-	5 (5
Zolpidem (Stilnoct)	-	-	-	2 (3)	-	-	-	-	-	4 (1)	-	5 (5
Flurazepam	-	1 (2)	-	-	-	-	-	-	-	-	-	
Unspecified	62 (13)	2 (4)	2 (6)	26 (36)	22 (11)	3 (9)	1 (6)	7 (14)	7 (7)	35 (11)	5 (22)	15 (15
Total	484 (100)	45 (100)	34 (100)	72 (100)	199 (100)	32 (100)	18 (100)	49 (100)	95 (100)	321 (100)	23 (100)	101 (100

Benzodiazepines were combined with other intoxicants in 936 cases (90 %), most frequently heroin 484 (47 %), ethanol (31 %) and amphetamine 199 (19 %).

Patients were brought to the A&E clinic by ambulance in 569 cases (55 %). On admission 47 patients (5 %) were comato (Glasgow Coma Scale (GCS) score ≤ 8), 619 (60 %) somnolent (GCS score 9–14) and 111 (11 %) had a respiratory rate < 1 During the course, 150 (14 %) patients were agitated, 42 (4 %) experienced anxiety and 41 (4 %) were hypotensive. Nalo (antidote against opioids) was administered in 187 cases (18 %), sedation in 13 (1 %) and flumazenil in 2 (0.2 %). The m observation period was 4 h 25 min (interquartile range 2 h 30 min – 6 h 11 min, range 3 min – 36 h 53 min). In 168 case (16 %) the patient was hospitalised in a somatic hospital, and in 20 (2 %) in a psychiatric unit. No patients died at the A clinic.

A respiratory rate of < 12/min was more common when benzodiazepines were combined with opioids, 101/601 (17 %) ca 10/436 (2 %) ($p < 0.001$), and naloxone was administered more frequently for this combination: 171/601 (28 %) cases v 16/436 (4 %) ($p < 0.001$).

Discussion

In substance abuse poisonings, benzodiazepines were very often taken in combination with other intoxicants – probably enhance the effect, counteract undesirable side effects or relieve abstinence symptoms. This is in line with other Europe studies based on a clinical assessment of toxic agents (10, 11). Even more cases prove to involve benzodiazepines, when assessments are supported by laboratory analyses (12).

Clonazepam was the dominant toxic agent. This stands in contrast to the Norwegian prescription pattern. Z-hypnotics accounted in 2014–2015 for two thirds of prescriptions, and 50 % more of both diazepam and oxazepam was prescribed clonazepam, and almost the same amount of nitrazepam as clonazepam (3). However, police seizures clearly reflect the distribution of the most frequently occurring benzodiazepines in substance abuse poisoning. Clonazepam accounted for the number of benzodiazepine seizures and 47 % of the quantity seized in 2014, followed by diazepam (20 % and 33 %) alprazolam (13 % and 18 %), while the quantity of z-hypnotics seized was minimal (13). Z-hypnotics seldom occur in sub abuse poisoning, probably because the intoxicant effect is relatively limited (5). Although Lyphout et al. found that natic prescription patterns correlated with the distribution of benzodiazepines in substance abuse poisonings (11), the intoxic potential and availability on the illegal market appear to be of greater importance than prescription by doctors.

Altered level of consciousness was the most prominent clinical finding, as expected (4, 5). Patients with assumed substa abuse intoxication are observed systematically at the OAEOC according to a locally developed procedure (14). Antidote i administered only in cases of respiratory depression. Most patients with respiratory depression had taken opioids in ad Naloxone is a safer antidote than flumazenil and is therefore administered first. The fact that flumazenil was only admir in two cases shows that naloxone was virtually always sufficient and that respiratory depression is rare in cases involvin benzodiazepines alone. If the respiratory rate does not improve, or if the patient has not woken within four hours and ca an account of themselves, the patient is sent on to hospital. Although the OAEOC has good observation possibilities and distance to hospital, we believe that our results and observations might be applicable to other A&E clinics with observat possibilities, and to hospital emergency departments.

Strengths and weaknesses

Toxicological screening is not carried out at the OAEOC. Diagnoses of toxic agents were accordingly based mainly on sel reporting, which may be deficient or incorrect owing to patients' altered level of consciousness, tablets of unknown cont from street and online sales, unwillingness to cooperate and/or fear of legal reprisals. There may also be variation in do record-keeping and in the inclusion and registration practice of data collectors.

Although the majority of substance abuse poisonings in Oslo are treated at the A&E clinic, the sickest patients are taken directly to hospital by ambulance (10). The picture of benzodiazepine poisonings in the capital is therefore not complete does the study cover benzodiazepine poisonings with suicidal intent, a far larger share of which are sent on from the A& to hospital (10). Our material is five years old, and the prevalence of the different intoxicants may have changed since th

Conclusion

Benzodiazepines are most often taken in combination with other intoxicants in substance abuse poisonings, most frequ heroin, ethanol and/or amphetamine. Clonazepam was the most prevalent benzodiazepine.

The article has been peer-reviewed.

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