Carisoprodol intoxication: a comprehensive review

Zulkifli Amin, Steven Zulkifly, Stephen Diah Iskandar

Abstract

Carisoprodol has been widely used as a muscle relaxant agent. In Indonesia, carisoprodol is well-known as carnophene/zenith. Many retailers sell this drug illegally, especially to sex workers to make them feel more relaxed. Due to high incidence of carisoprodol abuse, Drug Enforcement Administration (DEA) categorized it into Schedule IV. Knowledge about pharmacokinetic and pharmacodynamic of carisoprodol are essential to be understood for proper diagnosis and management. Until now, there are only a few case reports about carisoprodol intoxication and no guideline has been published. This article aims to provide an overview about carisoprodol intoxication, starting from the mechanism of action to its management. In the body, carisoprodol is metabolized to meprobamate by CYP2C19 liver enzyme. Diagnosis of carisoprodol intoxication is challenging because carisoprodol and meprobamate have opposite effect. Gastric lavage, administration of flumazenil and bemegride may be effective for acute intoxication case.

Key words: Carisoprodol, meprobamate, intoxication.

Introduction

Carisoprodol (N-isopropyl-2-methyl-2-propyl-1,3-propanediol dicarbamate, N isopropyl meprobamate) was developed by Dr. Frank M. Berger as a muscle relaxant agent. Carisoprodol was synthesized to create a better muscle relaxing property, safer, and less abuse potential than meprobamate. (1) Decades after carisoprodol invention, several researches reported that carisoprodol was converted to meprobamate in human body by liver. (2,3)

In Indonesia, carisoprodol is known as carnophene (zenith), which contained 200 mg carisoprodol, 160 mg paracetamol and 32 mg caffeine. Based on Indonesia's Drug Specialite Information (DSI/ ISO), carnophene is indicated to relieve low back pain, muscle spasm, tension type headache, dysmennorhea, and chronic arthritis. (4) In Sulawesi, carnophene is widely used by sex worker to make them feel less ashamed, more relaxed and confident to face their customer. (5)

The incidence of carisoprodol abuse have been reported worldwide, therefore Drug Enforcement Administration (DEA) classified carisoprodol in Schedule IV list as a drug can lead to physical and psyschological dependance. (6) In Norway, carisoprodol is one of the most abused drugs and causes fatality. (7-9) In Indonesia, many retailers sell carisoprodol illegally with average cost of carisoprodol is IDR 40,000 - 100,000 (US$3 - US$7.5) for 10 pills. Many cases of carisoprodol intoxication are found in Indonesia, but not recorded properly. (4,5)

Knowledge about pharmacokinetic and pharmacodynamic of carisoprodol are essential for proper diagnosis and treatment. Until now, there is no guideline about carisoprodol intoxication have been published, only several case reports discuss about this issue. The current review was conducted to explore studies about carisoprodol intoxication and its management.

From Division of Respirology and Critical Illness, Department of Internal Medicine, Faculty of Medicine Universitas Indonesia, Cipto Mangunkusumo National General Hospital, Jakarta, Indonesia (Zulkifli Amin, Steven Zulkifly, Stephen Diah Iskandar).

Address for correspondence:
Zulkifli Amin
Division of Respirology and Critical Illness, Department of Internal Medicine, Faculty of Medicine Universitas Indonesia, Cipto Mangunkusumo National General Hospital, Jakarta, Indonesia
Jalan Salemba Raya No. 6, Central Jakarta, Jakarta 10430
Email: zulkifliamin52@gmail.com

Pharmacokinetic of carisoprodol

Absorption

Two studies tried to determine pharmacokinetic properties of carisoprodol, using liquid chromatography-mass spectrometry (LC-MS) method. Simon et al measured plasma level of carisoprodol and meprobamate over 48 hours after administration of 250 and 350 mg carisoprodol, while the study conducted by Bramness et al measured plasma level of carisoprodol and meprobamate for 11 hours and 45 minutes after administration of 700 mg carisoprodol. (10,11) The comparison of pharmacokinetics properties is given in **Table 1**. Another study found that rapid gastrointestinal absorption of carisoprodol resulted in peak plasma concentration of 4-7 mg/l, which were achieved within 2-4 hours and onset of action within 30 minutes after ingestion. (12) Carisoprodol has a pKa of 4.2, which facilitate it to be highly absorbed in stomach and small intestine. (13)

Distribution

Carisoprodol is rapidly distributed to central nervous system. Protein binding of carisoprodol and meprobamate are approximately 60% and 25%, respectively. (13) There is no report of volume of distribution (Vd) for carisoprodol in human until now. Based on animal study by US National Toxicology program, estimated Vd of carisoprodol is 0.72 l/kg in rats and 0.65 l/kg in mice. An analysis using two-compartment pharmacokinetic model described that estimated Vd for carisoprodol in human is 0.93-1.3 l/kg, while for meprobamate is 1.4-1.6 l/kg. (14)

Metabolism

Carisoprodol is metabolized in liver by enzyme CYP2C19, produces its primary metabolite, meprobamate. Carisoprodol is also metabolized to hydroxy carisoprodol in much lesser extent by unknown enzyme. Both meprobamate and hydroxy carisoprodol are metabolized to hydroxy meprobamate, then partially conjugated. (15) The relationship between variation in CYP2C19 activity and metabolism of carisoprodol has been proven to be correlated with mephenytoin hydroxylation polymorphism (using probe drug S-mephenytoin). (3) Many drugs may interact with CYP2C19 and inhibit the metabolism of carisoprodol. Fluoxetine, fluvoxamine, omeprazole, and oral contraceptive drugs have been shown to reduce the metabolism of S-mephenytoin. (11,15-17)

Excretion

Carisoprodol is primarily excreted in urine. Less than 1% is excreted unchanged and 4.7% excreted as meprobamate over 24 hours after administration of 350 mg carisoprodol tablet. (18)

Mechanism of carisoprodol intoxication

After carisoprodol is metabolized by enzyme CYP2C19 in liver, it undergoes biotransformation to three metabolic products, such as hydroxy carisoprodol, hydroxy meprobamate, and meprobamate. In human, the main metabolic product is meprobamate. Meprobamate acts similar with benzodiazepine and barbiturate by modulating the function of γ aminobutyric acid A (GABAA) receptor. (19) GABAA receptor is an ionotropic receptor that directly connected with Cl-channel, thus the activation of this receptor causes the increase of chloride ion conductance and hyperpolarization of post-synaptic cells. (20) The impact of hyperpolarization of the cells is inhibition of intraneuronal transmission of descending reticular formation and spinal cord, which explained the sedative-hypnosis effect of carisoprodol. (21) Among other receptors, GABAA receptors are the major fast synaptic inhibition receptor in central nervous system. (20)

Meanwhile, four cases of carisoprodol intoxication showed similar manifestations to serotonin syndrome, including hypertension, tachycardia, choreiform movements, shivering and tremor. (22) These findings showed that carisoprodol had different mechanisms beside interaction with GABAA receptor. It hypothesized that carisoprodol had direct effect to central nervous system without conversion to meprobamate. However, the mechanism of this effect was still unclear.

GABAA receptors are the major fast synaptic inhibition receptor in central nervous system. GABAA receptor is member of cys loop ligand gated ion channels, including six α subunits, three β subunits, three γ subunits, three ρ subunits, as well as one ϵ, δ, θ, and π subunit. (20)

Many studies tried to solve the question why carisoprodol had different effect than its metabolite, meprobamate. Gonzales et al found that carisoprodol directly activate human α1β2γ2 GABAA receptor. However, this potentiation of GABA-gated currents was only occurred at micromolar concentration. On the contrary, high concentration of carisoprodol (millimole concentration) produced GABA inhibition, followed by rebound currents after termination of the drug. (23) This phenomenon could be explained by dose-dependent channel block of GABAA receptor that limits the maximum total current conducted, as found in other study with barbiturate compounds. (24,25) Even, in the absence of GABA neurotransmitter, micro-

molar concentration of carisoprodol causes rapid and reversible inward currents that can be blocked by picrotoxin, a non-competitive channel blocker for GABAA receptor. These inward currents are significantly higher than inward currents produced by meprobamate. (23)

Study in multiple combination of GABAA receptors found that meprobamate also had direct-gating and allosteric effect in α1-6β2γ2 GABAA receptor, with the largest effect in combination of α5 subunit. (26) However, carisoprodol is more potent and efficacious than its metabolite. Administration of therapeutic dosage is enough to activate GABAA receptor. (20)

In behavioral approach, carisoprodol has barbiturate-like effects, not solely due to its metabolite, meprobamate. Carisoprodol effect of locomotor activity depression lasting from 40 minutes to 2 hours in mice. The offset of motoric/behavior depression is parallel with the falling plasma concentration of carisoprodol. (23,27) This phenomenon proves that depressant effects of carisoprodol are not fully caused by meprobamate, considering the plasma half-life of meprobamate is 8 times longer. (19) Another study also found that inhibition of hepatic enzyme that decreased metabolism of carisoprodol caused longer duration of carisoprodol-induced paralysis. (28)

Another proof is drug discriminative study. Compounds like pentobarbital, chlordiazepoxide, and meprobamate can fully substitute for the discriminative stimulus effects of carisoprodol. The effects of carisoprodol are fully blocked by bemegride, a barbiturate antagonist, but not benzodiazepine antagonist. Meanwhile, flumazenil, a benzodiazepine antagonist but not barbiturate antagonist, fails to produce dose-dependent blockade for carisoprodol. (23)

Although carisoprodol has the same effect as barbiturate, carisoprodol is not acting at the barbiturate site receptor. Homomeric ρ1 GABA receptors and α1 glycine receptors are sensitive to carisoprodol, but insensitive to barbiturate. Moreover, W328M mutation at ρ1 GABA receptors confer sensitivity to barbiturate, but not carisoprodol. (23)

Clinical manifestation of carisoprodol intoxication

The symptoms of carisoprodol intoxication are simply classified into two different syndromes, depend on which substance is dominant, either carisoprodol or meprobamate. The clinical manifestations of each syndrome will be elaborated further in below. The half time of carisoprodol is 1-1.5 hours and meprobamate is 8 times longer, around 10 hours. Theoretically, the clinical manifestations will be initiated with acute carisoprodol intoxication syndrome then followed by meprobamate intoxication. However, none of the case reported these clinical manifestations. (19,29)

Acute carisoprodol intoxication causes decreases level of consciousness to coma or semi-coma. This high concentration of carisoprodol in serum (>25 μg/ml) also causes sign and symptoms of serotonin and anticholinergic syndrome that overlap each other. The clinical manifestations including nystagmus, pupil dilatation, decreased light reflex, diplopia, hyperthermia, tachycardia, elevated blood pressure, agitation, seizure, elevated muscle tone, hyper reflex, and involuntary movement (myoclonic jerk, choreiform, and myoclonic encephalopathy). (19,29)

Carisoprodol intoxication is easily occurred in patients with absence or decreased activity of CYP2C19, thus carisoprodol is metabolized slowly and the concentration of carisoprodol in serum is elevated to 4 times higher than normal people. This rare condition is found in 3-5% of Caucasian and African, and 15-20% of Asian. Omeprazole and fluvoxamine, a CYP2C19 inhibitor, can increase the carisoprodol concentration and decrease meprobamate concentration. Contrary, CYP2C19 inducers, such as aspirin and rifampin, decrease the carisoprodol concentration and increase meprobamate concentration. (30)

Prolonged agitation and seizure due to carisoprodol intoxication cause myoglobinuria and resulting in renal failure. A case report found agitation and muscle rigidity in patient, who consumed 35 grams of carisoprodol, lasting for 48 hours. Even after got treatment in hospital for 48 hours, the concentration of carisoprodol in serum was still categorized as toxic concentration (71 μg/ml). (31)

Meprobamate intoxication is defined as serum concentration above 60 μg/ml, which manifests in central nervous system depression, similar effect to barbiturate. Sign and symptoms in meprobamate intoxication including coma or semi-coma, respiratory depression, hypotension, muscle flaccid, and diminished physiology reflex. (32) The difference manifestations of carisoprodol and meprobamate intoxication were firstly realized when a child showed agitation after consuming 1200 mg of carisoprodol. (33) The effect of carisoprodol and meprobamate may be worsened if the patient also consumes alcohol, benzodiazepine, opioid, or tricyclic antidepressants. (34)

Laboratory diagnosis of carisoprodol intoxication

The methods to determine plasma carisoprodol and meprobamate level keep developing. Carisoprodol

and meprobamate are aliphatic compound without any significant ultraviolet absorbance or fluorescence. It is primarily measured by gas chromatography (GC) or gas chromatography-mass spectrometry (GC-MS). 35,36) These methods have limitations because carisoprodol and meprobamate are labile in heat. This problem can be overcome by hydrolyzed compounds with potassium hydroxide (KOH), and the hydrolysates are trimethylsilylated before GC-MS analysis. However, this method is time consuming and may cause delayed treatment. (37) The other solution is using liquid chromatography-mass spectrometry (LC-MS) equipped with electrospray ionization (ESI). (38)

The newest method to determine carisoprodol and its metabolite meprobamate is liquid chromatography with tandem mass spectral detection (LC-MS) using oral fluid sample. In the future, this method can be used for therapeutic drug monitoring, detection of driving under the influence of carisoprodol, pain management, and overdose detection. (39) Therapeutic serum level of carisoprodol ranging from 5-20 μg/ml. If serum level increases to 30-100 μg/ml, stupor and lethargy are manifested. Serum level is correlate with clinical effects. (40)

Postmortem analysis using GC-MS showed that distribution of meprobamate and carisoprodol in peripheral blood, central blood, and liver were different. If blood specimen is absence or contaminated, liver specimen may be used to approximate plasma concentration of meprobamate or carisoprodol. (41)

Acute management of carisoprodol intoxication

Until now, there is no published guideline for management of carisoprodol intoxication. A case report recommends gastric lavage soon after ingestion. Administration of activated charcoal can be given 1-2 hours after ingestion. Intubation and mechanical ventilation is considered if indicated. Intravenous fluid should be given to produce good urine flow and prevent kidney deterioration. Urine output should be monitored and targeted to 0.5-1 ml/kg/hour. (40)

Roberge et al prescribed flumazenil 0.2 mg intravenous bolus over 2 minutes in patient with acute intoxication carisoprodol with Glassgow Coma Score (GCS) 9. After administration, the patient become more alert within 2 minutes but still mildly somnolent. Five minutes later, second administration of flumazenil, with the same dose, reversed all sign of intoxication within 2 minutes. (40)

Naloxone, methylxanthines, and cholinergic agents were firstly investigated for benzodiazepine antagonist agents, but the studies did not show promising results. In 1981, flumazenil (1,4-imidazodiazepines) was introduced and showed significant outcome as a potent benzodiazepine antagonist. (42,43) As mentioned above, carisoprodol shows similar effect to benzodiazepine, which acts specifically at GABA receptor. Chloride ions are found abundantly in extracellular with sodium ion. When benzodiazepines bind to GABA receptors, GABAs are released from pre-synaptic site and open chloride channel in post-synaptic site, resulting in the influx of chloride ion into the nerve cell and cause hyperpolarization. (42)

Flumazenil acts as weak agonist and strong competitive antagonist to benzodiazepine receptors in central nervous system. (42) Flumazenil has minimal effect on relaxing muscle. The main effect is strong competitive antagonist to GABA receptor in central nervous system, but not in peripheral nervous system, causing inhibition of benzodiazepines effects. (44)

The lipophilic characteristic of flumazenil makes it rapidly enough to penetrate the central nervous system. However, the oral bioavailability after first pass metabolism and hepatic clearance is only 16%, so intravenous administration is the route of choice. Elimination half-life of drug is short, ranging from 0.7-1.3 hours. However, flumazenil has a large volume of distribution (0.63-10.06 l/kg). Flumazenil is excreted by urine, after undergoes complete hydroxylation by hepatic microsomal oxidative to inactive state and bound to glucuronide. (43)

One of the clinical indications of flumazenil is the management of benzodiazepine overdose. Several studies have shown that flumazenil intravenous administration alone could improve the consciousness in patients with benzodiazepine intoxication within minutes. The effect of flumazenil lasting from 1-5 hours. (43,44) Low dose flumazenil have been reviewed as therapy for benzodiazepine dependence. (45)

Recent study found that flumazenil was partially inhibit the carisoprodol effects. However, bemegride was reported can act as fully antagonist to carisoprodol and meprobamate effects. (19) Bemegride (β-ethyl-β-methylglutarimide) was firstly introduced in 1954 and have been widely used for barbiturate poisoning since 1957, with variable success. (46) In animal study, administration of 5-10 mg/kg of body weight bemegride antagonized the pentobarbital effect (barbiturate) but not the chlordiazepoxide (benzodiazepine). (47) In human study, administration of 50 mg bemegride intravenously was used to reverse the sedation effect of

0.5 gram of thiopentone, a short acting barbiturate drug. (48)

Discussion

The initial management of carisoprodol intoxication is prompt diagnosis following by appropriate treatment, to reduce the morbidity and mortality rate. In developing countries, intoxication diagnosis was still challenging due to limited resources of laboratory examination in health facilities. History of intoxication and clinical manifestation that suspicious to intoxication symptomps, could become strong predictors. The epidemiology of drug abuse in local area could help clinicians to diagnose the intoxication.

Drug abuse has been a serious concern due to affecting the physical and socio-economic well being of the country. The incidence of drug abuse in Indonesia was particularly high, however, the report of carisoprodol abuse was limited in several province. Public policies relating to drug abuse prevention and demand reduction should be made by government.

Conclusion

Carisoprodol is rapidly absorbed in gastrointestinal tract and its effects occur 30 minutes after ingestion. Carisoprodol is metabolized by CYP2C19 in liver to meprobamate. Both carisoprodol and meprobamate are central nervous system depressant by binding to GABAA receptor. Although meprobamate is carisoprodol metabolite, the clinical manifestations of intoxication are opposite to each other. Several studies reported that carisoprodol had benzodiazepine-like effect and others reported barbiturate-like effect. Supportive management (intravenous fluid, gastric lavage and activated charcoal) have been done in several cases and showed satisfying results. The use of flumazenil (benzodiazepine antagonist) or bemegride (barbiturate antagonist) as carisoprodol antidote may be considered to treat carisoprodol intoxication.

Conflict of interests

The authors declare that there is no conflict of interest regarding the publication of this article.

Table 1. Pharmacokinetic properties of carisoprodol and its metabolite, meprobamate, after administration of 250 mg, 350 mg, and 700 mg carisoprodol (10,11)

Properties	Simon, et al				Bramness, et al	
	250 mg carisoprodol		350 mg carisoprodol		700 mg carisoprodol	
	Carisoprodol	Meprobamate	Carisoprodol	Meprobamate	Carisoprodol	Meprobamate
Cmax (µg/ml)	1.24	1.84	1.78	2.46	3.7	4.1
Tmax (min)	90	216	102	270	83	270
T1/2 (min)	104.4	580.2	117.6	577.8	96	NA
AUC (µg/ml/h)	4.51	32.33	7.00	45.98	11.3	26.5

Legend: Cmax=maximum concentration; Tmax=transport maximum; T1/2=the half life of drug; AUC=area under the curve.

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