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CASE REPORT

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Adverse effects from counterfeit and mislabeled medicine containing tapentadol and carisoprodol

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Key Clinical Message

When self-administration with counterfeit or mislabeled medicine is suspected, comprehensive laboratory analysis should be preferred over immunoassay screening to avoid false negative results. Carisoprodol, which was formerly a popular muscle relaxant drug in many countries, has reappeared on illegal drug markets, and may cause an itching, purple-colored rash, even after a single dose.

KEYWORDS

adverse effects, carisoprodol, counterfeit medicine, meprobamate, tapentadol

1 | INTRODUCTION

Counterfeit and mislabeled medicines pose significant and increasing risks to the global public health. These illegitimate pharmaceuticals can contain incorrect or harmful ingredients, lead to improper dosages, or lack the necessary active compounds that is indicated on the packages of the product. Use of counterfeit medical products can lead to treatment failures, adverse reactions, and death.[1]

The illicit drug supply is unpredictable, and products found on the market may (i) contain the wrong active ingredients; (ii) contain no active ingredients at all; (iii) have fake labelling and labels that misrepresents the product; or (iv) have been produced under substandard conditions. This applies to both branded and generic medicines, and the World Health Organization (WHO) states that approximately 10% of medicines worldwide are counterfeited.[2] The estimated market size of counterfeit medicines ranges from $10 to $200 billion.[3]

Asia, particularly India, is a significant focal point for the production and distribution of counterfeit medicines, where estimated 35%–75% being manufactured in India.[1] The WHO also reports that about 50% of the drugs sold online via the internet are fake.[4] The drug types are mainly genitourinary, central nervous system, anti-infectives, cytostatic, and musculoskeletal drugs.[1]

Parallel with the opioid epidemic in the United States, a rise in counterfeit opioid medications has been recorded, for example tablets sold from pharmacies as "oxycodone" containing fentanyl or heroin.[5] Counterfeit tablets may be manufactured to match well with existing, registered drugs and having similar physical identification parameters and unique imprints.[6] This is a pervasive problem, particularly in the US, resulting in a rise in fatalities caused by overdoses of "non-pharmaceutical fentanyl."[7] However, the uncontrolled use of opioids is now a concern globally and pose a serious threat to public health.[8]

This case report details the adverse effects experienced by a patient who self-administered a pain-relieving counterfeit medication, believed to contain tramadol, but containing the opioid tapentadol and the muscle relaxant carisoprodol. To the best of our knowledge, this is the first case describing a counterfeit medication containing both tapentadol and carisoprodol.

2 | CASE HISTORY

In April 2024, a 16-year-old Danish teenager was referred to substance abuse treatment due to the use and dependence on non-prescribed opioids. During the initial consultation, the patient described both withdrawal symptoms and cravings when not taking opioids. In the months leading up to the referral, the patient had been using oxycodone and tramadol, with tramadol being the primary substance. Prior to the referral to treatment, urine testing was performed at a hospital with an unspecified urine panel test, yielding negative results.

2.1 | Clinical presentation

At the first consultation, the patient appeared slightly intoxicated and uncertain about pursuing treatment. The following morning, the patient called the department, expressing concern about the effects of tramadol purchased from the illegal market. Symptoms associated with the ingestion of tablets the previous evening included weakness in the legs, cyanosis of the lips, chest pain, and a rash on the chest and bilateral on knees. Acute hospitalization was recommended, but the patient declined as some symptoms subsided. An urgent appointment was scheduled. Objectively, the patient appeared opioid-intoxicated with miosis, slow speech, but normal respiration and gait. Despite the intoxication the patient was alert, oriented in time, place, and personal details. A supervised urine sample was obtained and tested with a 12-panel urine drug test (Ferle ApS, Denmark) including opiates, methadone, oxycodone, fentanyl, tramadol, and buprenorphine, which was negative. Over the next few days, repeated supervised urine tests were negative despite visible obvious intoxication.

On the fifth day, the patient presented with withdrawal symptoms, including mydriasis, flu-like symptoms indicative of opioid withdrawal, and strong cravings. A urine sample was sent for extended laboratory analysis (see below), and the patient voluntarily provided two tablets for analysis. Despite the negative on-site urine tests, the patient was started on a low dose of buprenorphine, as the risk of overdose from the illegal tablets was deemed too high if treatment was not initiated. The patient reported severe intoxication with cyanosis of the lips and rash when taking the illegal tablets and marked fatigue the following day. The nummular rash, just above both knees extending over the patella, was purple and darkened in the evenings.

Following the initiation of buprenorphine treatment (0.4–2.0 mg in five steps during the first 24 h), the patient ingested the illegal tablets twice. This reduced the effect of the substitution medicine leading to side effects such as rash, chest pain, and spending the entire next day sleeping. Due to these side effects, the patient underwent various blood tests, including an ECG. Paraclinical tests showed mild leukopenia with decreased neutrophils. Leukocytes were 3.4×10^9/L (normal range 4.4–10.5×10^9/L), and neutrophils were 1.53×10^9/L (normal range 2.0–9.6×10^9/L). There was a slight decrease in alkaline phosphatase at 42 U/L (normal range 50–120 U/L). No abnormalities were detected in other hematological, renal, hepatic, or metabolic tests. The ECG showed sinus rhythm with a heart rate of 77/min and a QTcB of 443 ms. The decreased neutrophils were interpreted as induced by the ingested illegal medication.

2.2 | Outcome

The patient is currently stabilized on sublingual buprenorphine (resoriblets), 2.4 mg daily. At this dosage, the patient withdrawal symptoms were eliminated, but severe cravings for the high, indicated the risk of relapse into illegal use and potential overdose being significant.

3 | METHODS AND RESULTS (DRUG TESTING)

3.1 | Laboratory urine drug testing

Laboratory analysis was performed with high-performance liquid chromatography and tandem mass spectrometry (LC–MS/MS). Creatinine concentration was 4.0 mmol/L. The sample was positive for tapentadol (40 ng/mL) and the major metabolite tapentadol glucuronide (1173 ng/mL). Other opiates/opioids, including tramadol and the main metabolite O-desmethyltramadol (at cutoff levels 100 ng/mL) were not detected.

3.2 | Chemical analysis of tablets

The patient provided a sample of the medicine for chemical analysis. Two tablets were obtained in original blister packaging labeled "Tamoll X 225 mg USA." The blister package, shown in Figure 1, also included a possible batch identification imprint (007 M12) and an expiration date (22E/11 25). The original packaging and leaflet were unavailable because the drug was obtained from the illicit market in Denmark. The company reportedly behind the product is Royal International Co., based in Punjab, India, although this information may be unreliable. Several Indian websites offer the purchase of these drugs to various countries. The product "Tamoll X 225 mg" is

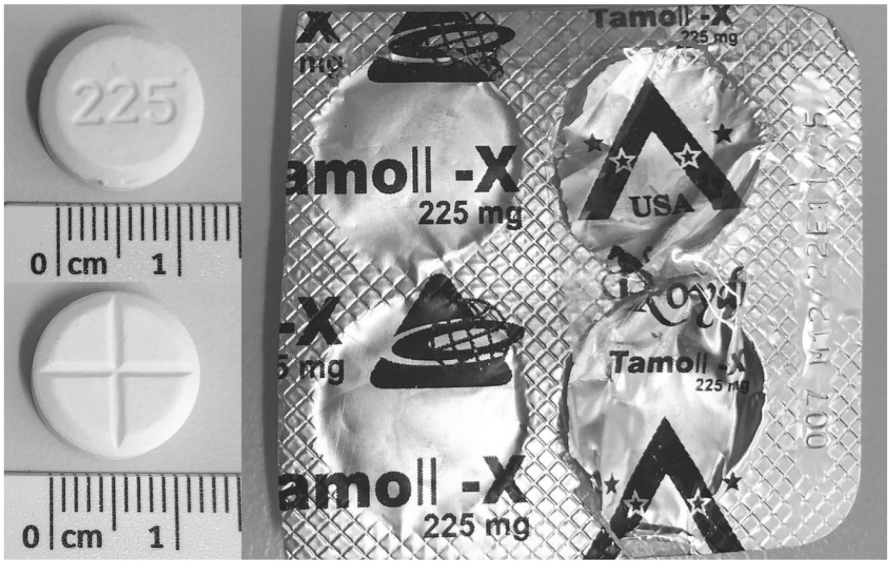

FIGURE 1 Right: Photo of original blister packaging labeled "Tamoll X 225 mg USA." Left: Tablet (front and back side).

listed on several webpages and is marketed as containing Tramadol.[9] When the product is spelled "Tamol X 225 mg," several European websites offering the product can be found.

A tablet was carefully pulverized with a mortar, and a stock solution equivalent to 1 mg/mL of tablet powder was prepared in methanol. A dilution of this stock solution was analyzed by gas chromatography and mass spectrometry (GC–MS). The chromatogram showed intense peaks from two compounds, tapentadol and carisoprodol, that were unambiguously identified using a library mass spectrum search.

4 | DISCUSSION

A case from literature has shown that Tramadol tablets found on the Egyptian market, labeled Tamol-X, Tramadol-X, Tee-doll, Super tramadol-X and Tramajack, also contained Alprazolam, Chlorpheniramine, Diphenhydramine, or Paracetamol, besides an amount of tramadol, that in some cases also deviated from the labeled dosage (mg). The authors stated Royal International Co. in India as the source of these counterfeit products.[10] However, there are no clear cases reported in the literature of medicine being mislabeled as containing tramadol when it did not actually contain that drug.

4.1 | Tapentadol

Tapentadol, an opioid with moderately strong analgesic effect, was initially not considered associated with substance abuse. Moreover, there was a notable trend of reduced online discussions about tapentadol among recreational drug users on internet forums.[11] However, in most states of India where tapentadol is available without a prescription, there has been a rise in reports of addiction, abuse, and misuse, including injection of crushed tablet solutions.[12–15] In Australia, the incidence of postmortem detections in deaths involving mixed-drug toxicity is increasing concurrent with the growing number of tapentadol prescriptions.[16]

The demand for illicit or counterfeit medications containing tapentadol appears to be on the rise, particularly in Asia, with the potential for this trend to extend to counterfeit products containing tapentadol. Despite tapentadol being considered an atypical opioid and not a primary concern for individuals seeking treatment for opioid use disorders in certain regions,[17] the diversion of tapentadol pharmaceuticals and the possible emergence of other tapentadol-containing products may go unnoticed in urine drug testing, as standard immunoassays do not detect or cross-react with tapentadol.

4.2 | Carisoprodol

Carisoprodol is a drug used for musculoskeletal pain. The abuse liability of carisoprodol involving addiction followed by severe withdrawal symptoms during abstinence has been known for decades.[18–20] Drug users seek the sedating, relaxant and anxiolytic effects of the drug, and carisoprodol has been reported in combinations with for example benzodiazepines. Reports from Norway has described carisoprodol as an addictive drug and in 2008, after a debate about its properties,[21–23] it was withdrawn from the market. The European Medicines Agency (EMEA) decided in 2007 that all medical products with carisoprodol should be suspended.

In India, abuse of carisoprodol was reported as early as 1993,[24] and in 2013 a paper warned against carisoprodol, stating that misuse was underrated and unrecognized, as national surveys did not include the drug.[25] Earlier, in 2002, in report from the US, the authors came to the same conclusion.[26]

4.3 | Meprobamate

Adverse effects can also be mediated by meprobamate, the major and active metabolite of carisoprodol. Meprobamate is an anxiolytic drug which was previously widely used but later replaced by safer benzodiazepines. Among less common effects are skin rash, hives, and itching, as well as weakness and unusual tiredness, which were also experienced by the patient in the present case.

In 1969, itching and colored rash was reported as an adverse effect in a patient with a prescription to meprobamate. The author described: "After two days, haven taken only two to three tablets, he noticed itching and pinkness in the bends of the elbows. This was accompanied by shivering and feeling unwell. During the next few days, he continued to take the tablets to a total of about eight. The rash rapidly became purpuric and spread to the inner thighs and behind the knees. He was admitted to hospital for investigation and the rash subsided in a few days without treatment."[27]

Several publications in the late 1950s (not referred to here) also report rapidly occurring skin reactions ("purpuric rashes" with "intense itching,") after only one dose of meprobamate. The cutaneous effects were described in detail by Friedman and Marmelzat in 1956.[28]

4.4 | Two active substances in one formulation

Medical drug products containing two or more active substances are referred to as fixed-dose combinations (FDCs). The risks associated with FDCs include pharmacokinetic and pharmacodynamic interactions, overdosing, unforeseen reactions, and difficulties in identifying the cause of adverse events. While FDCs may be licensed, medical authorities require extensive evidence of clinical efficacy and justification for their approval. In the present case, there is no globally recognized medical FDC product that combines tapentadol and carisoprodol.

Ingestion of tapentadol and carisoprodol can lead to CNS depression effects, including drowsiness, dizziness, respiratory depression, and in severe cases, profound sedation, coma, and death. Tapentadol can cause constipation, which may be exacerbated by carisoprodol, which also has constipation as a potential side effect. Additionally, both medications can cause headaches. Carisoprodol is contraindicated with alcohol intake, and several drug interactions have been reported, including those with opioids and certain psychopharmacological agents.

The presence of both tapentadol and carisoprodol in a single counterfeit medication, purposefully manufactured in India, seems to be driven by a local demand in India for these specific compounds. It poses an elevated risk to public safety, that this falsely labeled counterfeit product (Tamoll X 225 mg) is being distributed to Europe.

4.5 | Implications for drug testing

We strongly encourage clinical laboratories with experience in substance abuse and drug analysis to perform analyses of suspicious substances that patients share with clinicians. It is essential that these laboratories can perform unambiguous substance identification. In Denmark, forensic departments are not obligated to conduct analyses that are not requested by the police. This means that public institutions, including treatment facilities, clinical departments, and so forth, may lack analytical support in cases where unidentified medication has been found, confiscated from patients, or voluntarily submitted by concerned patients. It is also important to note that immunochemical screening techniques (urine drug panel tests, urine sticks) are not suitable for the task. These products are designed to detect substances at very low concentrations (sub-ppm) in urine and are often manufactured to measure the metabolites of the substances.

Furthermore, it is crucial that clinical laboratories involve forensic departments and the health authorities if they observe new psychoactive drugs (NPS) or suspect that particularly dangerous or toxic products may be circulating in the community, posing a potential risk to public health.

4.6 | Non-medical use of tramadol is rising

The synthetic opioid tramadol is often perceived as less addictive, and not all countries classify it as a controlled substance. Numerous publications have documented the global rise in both medical and non-medical use of tramadol, with reports from regions such as the United States,[29] Africa,[30] Iran,[31] and Europe.[32] This trend has resulted in significant public health challenges, including issues with

drug rehabilitation, cases of overdose, emergency department visits, and fatal intoxications.

4.7 | Diagnosis and treatment

1. Laboratory analyses of urine and tablets performed with proper analytical methods, but *not* urine screening with immunoassays, provided an identification of the drugs of concern.
2. Appearance of a purple-colored rash, as described above, can potentially be used as a diagnostic marker of carisoprodol/meprobamate administration.
3. The purpuric rashes reported in literature disappeared after termination of the use of carisoprodol/meprobamate.
4. Treatment of abstinence and drug craving after the combined intake of tapentadol and carisoprodol was successfully treated with buprenorphine.

5 | CONCLUSION

Addressing the risks involving counterfeit medicine requires public awareness to protect patients. It is crucial for drug users to be cautious as counterfeit pharmaceuticals may contain unknown and potentially dangerous ingredients that can pose severe health threats. In cases of patients' self-medication with opioids, adolescents may represent a particularly vulnerable group of people.

This clinical case calls for increased awareness of tapentadol and carisoprodol, as a potential unsafe drug mixture in counterfeit medications, substituting other opioids, such as tramadol. It is important that carisoprodol and the metabolite meprobamate are added as target compounds in comprehensive, laboratory analysis used in clinical toxicology. Furthermore, clinicians should not trust simple immunoassay tests in pain management of patients that may be susceptible to self-medication.

AUTHOR CONTRIBUTIONS

Gitte Plæhn: Conceptualization; data curation; investigation; writing – original draft. **Thomas Fuglsang:** Writing – review and editing. **Peter Hindersson:** Writing – review and editing. **Torben Breindahl:** Conceptualization; data curation; investigation; writing – original draft.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflict of interest to be disclosed.

DATA AVAILABILITY STATEMENT

Data that supports the findings of this study are available from the authors upon reasonable request.

CONSENT

Written informed consent was obtained from both parents of the patient to publish this report in accordance with the journal's patient consent policy.

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