Drug-Related Problems Following Use of Clonazepam Oral Drops

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Liquid medications are crucial during titration and tapering phases. Meanwhile, devices used for measuring liquids (eg, droppers, cups, syringes, and spoons) have been associated with a potential risk of under- or overdosing,[1] which is particularly critical for central nervous system drugs.

In the last few years, different drug-related problems associated with clonazepam oral drops have been reported to our local postmarketing surveillance services. We present an investigation to determine if such events were associated with any product quality deviation.

Reported Cases

The first patient reported that since the first use of the medication, he could not measure the prescribed doses because the drug was delivered in streams instead of drops, resulting in imminent overdosing. He also stated that when switching to the same medication from a different manufacturer, the drops were delivered properly.

The second patient reported a suspected therapeutic failure when using the same medication, with no further details. A retrospective gathering of information from the manufacturer's customer service department revealed 16 complaints regarding this medication during a 2-year period after the first report.

Investigation

A representative sample from 3 batches of the product under investigation—glass bottles with dropper insert containing clonazepam oral solution—was obtained and evaluated for quality deviations by the state's surveillance laboratory (batch A: 10 bottles, B: 4 bottles, C: 10 bottles).

First, clonazepam potency was evaluated by high-performance liquid chromatography. The product complied with the test if the solution contained 90%–110% of the labeled amount of clonazepam.[2]

Second, a dripping test was performed. The test was carried out with the bottle on the inverted vertical position (0°), allowing a gravity flow system. Briefly, the amount of drug per drop was determined considering clonazepam potency, the number of drops per mL, and the weight of 1 mL for each bottle (10 bottles).[3]

The product met the requirements if individual values of the amount of drug per drop were between 85% and 115% of the labeled amount and relative standard deviation (RSD) was less than 6% (10 bottles).[3]

We found that solutions presented 97.7%, 96.4%, and 97.8% of the labeled amount of clonazepam (batches A, B, and C, respectively). Batch A presented inconsistency between delivered drops and thus failed the dripping test (5 bottles out of the 85%–115% range and RSD = 12.2%, 10 total bottles). The amount of clonazepam per drop ranged from 82.1% to 118.8% among the bottles from this batch.

Two bottles from batch B delivered streams instead of drops when first turned upright to initiate dripping. The dropper inserts were not centralized in these bottles. Also, the dripping was rapid, and it was difficult to avoid the delivery of an extra drop at the end of the procedure. Three other bottles from batch C were extremely full of liquid, thus the dripping was impaired.

Although all batches fulfilled the requirements for clonazepam potency in the solutions, dose delivery was affected due to dropper malfunctions.

Discussion

Our investigation and prior case studies[4,5] have shown that dropper-related issues can cause significant dosing errors. A very severe outcome was reported in a case[4] involving the administration of codeine drops in children. It was found that codeine dose ranged to a great extent when delivering 10 drops from a dropper bottle (around 90% of the labeled amount), causing a drug overdose.

The dropper quality issues found by our investigation can be highly linked to the reported events described here. Accuracy and precision of delivered doses must be ensured by manufacturers so that droppers meet their quality standards for functionality and consistency with the prescribed doses, supporting a safe and effective psychopharmacotherapy with liquid oral drugs.

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