Cyclobenzaprine

Cyclobenzaprine (Flexeril®) is a tricyclic compound first synthesized in 1971 for use as a centrally acting muscle relaxant. The drug is indicated for relief of the acute pain associated with acute muscle spasms. Cyclobenzaprine is supplied in 10 mg. tablets with a recommended daily dose range from 30 to 60 mg. Therapeutic levels achieved with 30 mg per day provide mean peak and trough plasma concentrations of 0.022 µg/mL and 0.015 µg/mL, respectively.

Chemical Structure and Metabolism

Cyclobenzaprine is a tricyclic compound structurally similar to the antidepressant amitriptyline. Cyclobenzaprine undergoes demethylation to form the major metabolite norcyclobenzaprine. Similar to the metabolism of amitriptyline to nortriptyline, the demethylated metabolite is pharmacologically active.

![Chemical Structure Diagram](https://example.com/diagram.png)

Cyclobenzaprine and its major metabolite norcyclobenzaprine differ from amitriptyline and its metabolite nortriptyline by only a single double bond in the central cycloheptyl ring. This explains the similar physiological properties and physiological effects as well as the difficulty in detection with amitriptyline. The drug is extensively metabolized in the liver via the hepatic P-450 isoenzyme CYP3A4. Drugs that induce this enzyme or genetic variations may potentiate toxicity.

Analysis

The similarity of the chemical structure of cyclobenzaprine with amitriptyline and other antidepressants leads to difficulties in differentiation. It may be difficult to discriminate between the two analytes with many analytical methodologies utilized for comprehensive drug detection and identification. Cross-reactivity occurs with all commercially available immunoassay kits that detect the tricyclic antidepressants. For consistent and correct identification of cyclobenzaprine, a confirmation technique which can accurately distinguish between cyclobenzaprine and amitriptyline must be used. (1-3)
Gas chromatography with flame-ionization, nitrogen-selection, or mass spectrometry can be used for qualitative screening, confirmation and quantitation of cyclobenzaprine and metabolite. Dependent upon the parameters used, similar retention times to amitriptyline and metabolites may occur. Confirmation by gas chromatography/mass spectrometry (GC/MS) in the scan mode produces similar mass spectra ions: 58 (base peak), 215 and 202. By eliminating the 58 ion from the scan and beginning the scan from 60 to 500 amu, cyclobenzaprine is detected by the 215 base peak and amitriptyline by the 202 base peak. (4-5)

Cyclobenzaprine can be qualitatively detected and identified by commercial thin layer chromatography. However, the similar reference factor, Rf value, and detection stage staining characteristics to amitriptyline cause difficulties in discrimination between cyclobenzaprine and amitriptyline. With commercial thin layer chromatography kits, cyclobenzaprine has a similar retention time as amitriptyline, 0.58 and 0.56, respectively. Both analytes exhibit similar detection stage staining characteristics. However, in stage III cyclobenzaprine has a brilliant orange fluorescence while amitriptyline fluoresces pink. The intensity of fluorescence is concentration dependent and at low concentrations it may be difficult to differentiate between the two drugs. Elimination of the formaldehyde exposure step, which alters the color characteristics of both drugs, may enhance identification. (4-6)

High pressure liquid chromatography (HPLC) is also used for qualitative screening, confirmation, and quantitation of cyclobenzaprine. Depending upon the chromatographic parameters and type of column used, cyclobenzaprine may have similar retention time as amitriptyline with HPLC. To eliminate the possibility of interference due to co-elution, UV spectral detection with variable wavelength monitoring or photodiode array detection can be used to readily differentiate cyclobenzaprine from amitriptyline based on differences in absorbance spectra, (4,7-8). The automated HPLC REMEDI® Drug Profiling System, which utilizes a fast-scan ultraviolet detector, can correctly identify cyclobenzaprine and amitriptyline due to markedly different absorbance spectra despite identical relative retention times. (4)

Toxicity

Cyclobenzaprine has side effects similar to tricyclic antidepressants including anticholinergic effects, hallucinations, delusions, cardiac arrhythmias and seizures. Elderly patients are at increased risk due to alterations of the hepatic P450 system. Physostigmine has been used successfully to control the atropine effects. Drug levels of 0.03 – 0.35 µg/mL were detected in victims of overdose, while fatal blood concentrations range form 0.46 to 0.53 µg/mL. (9-11)
References:


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