# Excretion of Compound M-11 and Its Metabolites with Urine and Feces in Rats

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The excretion of compound M-11 and its metabolites with the urine and feces was studied in rats after intraperitoneal and oral administration in a dose of 25 mg/kg. Experiments showed that 1% metabolites were detected in excretions over 24 h irrespective of the route of administration, while the initial compound was not found even in trace amounts.

**Key Words:** *excretion; compound M-11; metabolites*

Experimental pharmacokinetics and biotransformation of afobazole is studied in detail. The drug undergoes intense biotransformation with the formation of several main metabolites, among which the levels of M-11 metabolite are the highest. The absolute values of tissue availability of afobazole and M-11 in the brain are close [2]. Compound M-11 has been synthesized at the Department of Chemistry of V. V. Zakusov Institute of Pharmacology.

Analysis of the excretion of the test compound is an important stage of pharmacokinetic studies. We identified and measured M-11 and its metabolites in the urine and feces of rats using mass spectrometric characteristics and synthetic reference samples.

## MATERIALS AND METHODS

The study was carried out on outbred male albino rats (200±20 g) from Stolbovaya Breeding Center of the Russian Academy of Medical Sciences. The animals were kept under standard vivarium conditions at 12:12 h light:dark regimen. Compound M-11 in water solution was injected intraperitoneally or was administered orally in a single dose of 25 mg/kg.

Compound M-11 and its metabolites were extracted from excretions with diethyl ester. A 20-fold volume of diethyl ester was added to 1 ml urine specimens and the mixture was shaken for 15 min.

The feces were dried in a hot cabinet at 50°C for 1 h. The feces (50 mg) were then fragmented, suspended, and homogenized in 1 ml pure water. A 20-fold volume of diethyl ester was added to the homogenate and the mixture was shaken for 15 min. Excretion was carried out twice in all cases.

Mass spectra of metabolites and synthetic reference specimens were recorded by HPLC with tandem mass spectrometry (HPLC-MS/MS) on an Agilent 1200 Series system (Agilent Technologies). Specimens of the rat urine and feces containing M-11 and its identified metabolites (the synthesis was carried out by T. Ya. Mozhaeva, Cand. Chem. Sci.) analyzed by HPLC on a Beckman Coulter chromatographer fitted with an isocratic pump System Gold 127 Solvent Module, an ultraviolet detector System Gold 166 Detector with alternating wavelength, and a computer with chromatogram processing software. The method for measurements of M-11 compound and its metabolites was described previously [2].

## RESULTS

The initial compound was not detected in the daily urine and feces, and we concluded that the drug was

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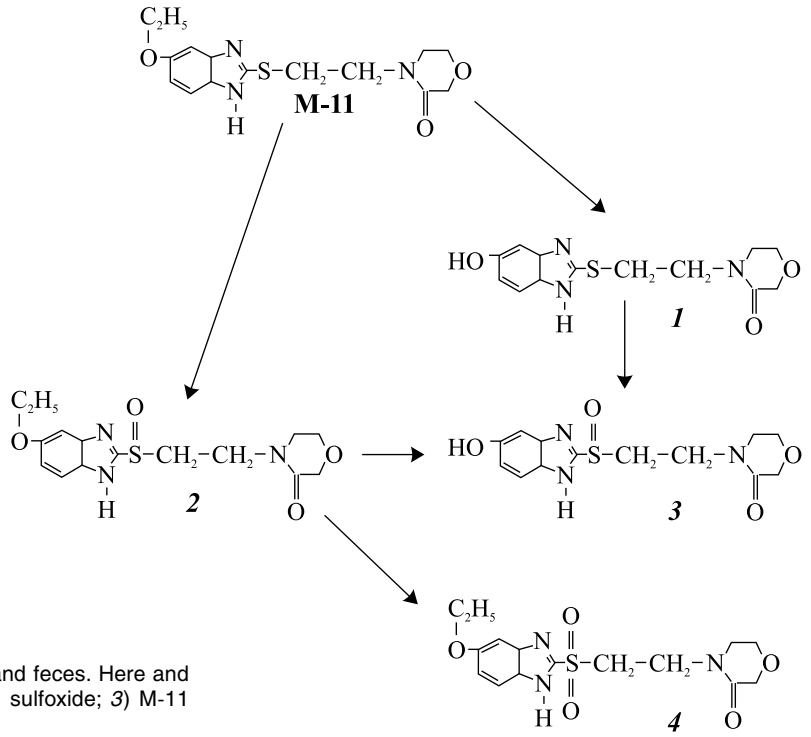


**Fig. 1.** Metabolism of compound M-11 in the rat urine and feces. Here and in Figs. 2, 3: *1*) M-11 hydroxylated derivative; *2*) M-11 sulfoxide; *3*) M-11 hydroxylated sulfoxidized derivative; *4*) M-11 sulfone.

completely absorbed from the gastrointestinal tract into systemic circulation. Four M-11 biotransformation products were identified in the rat feces by molecular ions and synthetic evidence-reference specimens: M-11 hydroxylated derivative, M-11 sulfone, M-11 sulfoxide, and M-11 hydroxylated sulfoxidized derivative (Fig. 1).

Chromatograms of daily urine and feces of rats showed peaks that were absent in control specimens and that presumably corresponded to metabolites of unknown structure. Internal standardization showed that the sum of chromatographic peak areas for metabolites of unknown structure was about 5%.

Hydroxylated derivative could be regarded as the main metabolite of M-11 compound. Its content in the urine was 0.41% of the administered dose. Sulfoxide M-11 was also detected in the urine, its content was 0.19%. Urinary levels of M-11 sulfone and hydroxylated sulfoxidized derivative were much lower (Figs. 2 and 3). These results confirmed published that benzimidazole derivatives were eliminated largely due to formation of hydroxylated metabolites by the aromatic ring [3,4].

A total of 0.68% (of the dose administered) identified metabolites were excreted with the urine and 0.37% with feces over 24 h (Figs. 2, 3). These results were in line with published data on benzimidazole derivatives excretion. For example, 80% omeprazole dose was excreted with the urine in the form of metabolites and a smaller fraction with feces [5]. Similar

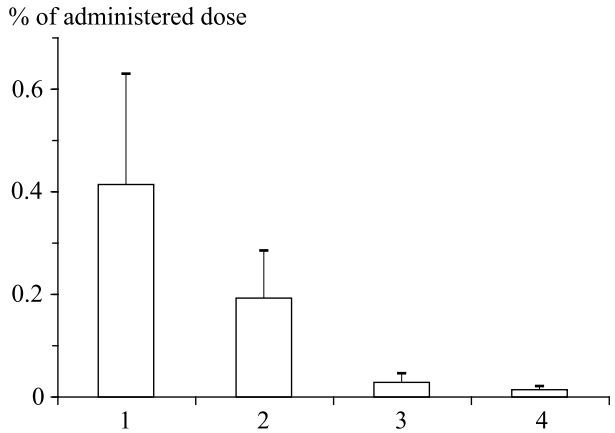


**Fig. 2.** Content of metabolites in daily urine after oral dose of M-11 compound.

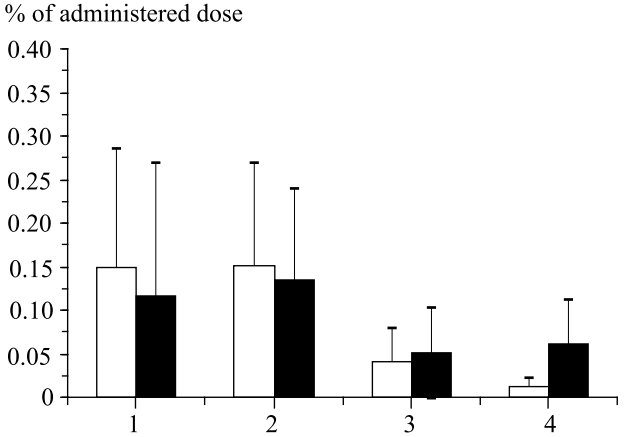


**Fig. 3.** Content of metabolites in daily feces after intraperitoneal (light bars) and oral (dark bars) administration of the drug.

data were reported for afobazole, lansoprazole, pantoprazole [1,4,6].

A previous study on rats has shown that 42.1% all metabolites of oral and intraperitoneal afobazole dose of 25 mg/kg were detected over 24 h in excretions [1]. On the other hand, only ~1% M-11 metabolites were detected in daily urine and feces of rats after similar administration of M-11 in the analogous dose. This difference was presumably caused by much more intense biotransformation of afobazole in comparison with M-11 compound.

Analysis of M-11 metabolite excretion processes indicated that this substance was released almost exclusively due to its biotransformation in the liver. The summary release of metabolites within 24 h with the urine in rats was 2-fold higher than with feces and the main trend of M-11 compound biotransformation was the formation of metabolites hydroxylated by the benzimidazole cycle aromatic ring.

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