Excretion and Metabolism of Mitoxantrone in Rabbits

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ABSTRACT

The hepatic clearance of mitoxantrone was evaluated in rabbits using both bile-duct cannulated animals and freshly isolated hepatocytes in suspension or in primary culture. Mitoxantrone metabolic behavior was assessed by high-performance liquid chromatography using a method which specifically resolved mitoxantrone from its mono- and dicarboxylic acid derivatives. Excretion of mitoxantrone in bile and urine was studied over a 6-h period of observation following i.v. bolus injection of 0.04, 0.20, and 1.0 mg [14C]mitoxantrone/kg. Bile route represented the main excretion pathway for mitoxantrone and its metabolites—mainly the monocarboxylic acid derivative. Biliary excretion was very rapid (maximum biliary concentration achieved 9 to 18 min following drug administration) and amounted to 29.5 ± 9.3%, 27.6 ± 7.9%, and 28.3 ± 3.8% of administered drug, respectively. Urinary excretion amounted to 7.3 ± 0.2%, 7.1 ± 4.6%, and 6.0 ± 1.5%, respectively. Both biliary and urinary excretions of mitoxantrone and its metabolites remained linear over the range of concentrations routinely used in clinic. Metabolism of mitoxantrone was first studied using rabbit hepatocytes in suspension. Since metabolic rate was slow under these incubation conditions (observation period, 1 h), mitoxantrone metabolism was investigated in primary cultures of rabbit hepatocytes. Mitoxantrone was rapidly accumulated within the cells and metabolized to its various metabolites which rapidly effluxed in the extracellular medium. After a 48-h exposure of hepatocytes to a broad range of mitoxantrone concentrations (1 to 20 μM), it could be seen that (a) drug accumulation and metabolism did not exhibit saturation processes, (b) mitoxantrone was the main intracellular form, while (c) metabolites rapidly effluxed in the extracellular compartment and (d) the monocarboxylic acid derivative represented the main extracellular metabolite. This data demonstrates the important role played by the liver in the pharmacokinetic behavior of mitoxantrone and suggests a careful drug monitoring in patients with severe liver dysfunction.

INTRODUCTION

Mitoxantrone (Novantrone®; 1,4-dihydroxy-5,8-bis[(2-hydroxyethyl)amino]ethyl)amino)-9,10-anthracenedione dihydrochloride; NSC 301739) is a new anthracyclene derivative currently used for the treatment of breast cancer and of patients with acute nonlymphocytic leukemia (1–3). This anticancer drug has shown antitumor activity equal or superior to that of Adriamycin in a number of animal tumor systems and in the tumor stem cell assay (4, 5).

Different laboratories have investigated the pharmacokinetic behavior of mitoxantrone following various schedules of administration (6) with a view to optimizing the clinical use of this compound. However, few attempts have been made to elucidate its metabolism and the enzyme systems responsible for its disposition. Different authors have investigated the elimination pathways of mitoxantrone in different species (7–10) including Xenopus (11, 12) or in primary cultures of human hepatocytes (14). Major metabolites of mitoxantrone recovered in urine of humans (11, 12) or in primary cultures of human hepatocytes (14) were the mono- and dicarboxylic acids resulting from oxidation of the terminal hydroxyl groups of the side chain(s) (12). This report investigates (a) the elimination pathways of mitoxantrone and its metabolites in bile-duct cannulated rabbits and (b) the kinetics of mitoxantrone metabolism in primary cultures of rabbit hepatocytes.

MATERIALS AND METHODS

Drugs and Reagents. Mitoxantrone (M, 517.4), its mono- and dicarboxylic acid derivatives as well as [14C]-labeled mitoxantrone were generously supplied by Lederle Laboratories (Pearl River, NY). Radioactive [2-hydroxyethyl]-14C-mitoxantrone (specific activity, 11.2 mCi/mmol) was 95% radiochemically pure as assessed by HPLC4 and was used without further purification. Type IV collagenase was purchased from Sigma Chemical Co.

Chromatographic solvents were of analytical grade. Other chemicals and reagents were obtained from regular commercial sources.

In Vivo Experiments. Experiments were performed in male New Zealand rabbits weighing 1.8–2.5 kg. Animals were anesthetized with urethane (2.0 g/kg) and kept at constant body temperature with warming lamps throughout the experiment. Preloading was achieved by continuous infusion into the left ear vein of a solution containing 0.3% NaCl and 1.3% glucose at 1.0 ml/min (15). A laparotomy was performed and the bile duct was cannulated with Vygon tubing (0.5-mm internal diameter) and tightly ligated. Bile samples were drawn at selected times after the i.v. injection and up to the sixth hour. Urine was collected by way of a vesicourethral catheter.

[14C]Mitoxantrone was injected as a bolus (never exceeding 2 min) in the left ear vein. Injected doses were 0.04, 0.20, and 1.00 mg/kg.

In Vitro Experiments. Hepatocytes prepared from male New Zealand rabbits weighing 0.6–1.0 kg, were obtained by a modification (16, 17) of the collagenase perfusion technique of Berry and Friend (18). Prior to experimentation, animals were anesthetized with urethane (2.0 g/kg). In brief, the liver was successively perfused with EGTA-supplemented Kreb's Henseleit buffer and EGTA-free Kreb's Henseleit buffer, followed by single-pass perfusion with 500 ml of the same medium containing Sigma Type IV collagenase (0.5 mg/ml). The softened liver was excised and the hepatocytes were resuspended in Leibovitz L-15 medium containing 0.25% gelatine. The hepatocytes were separated from nonparenchymal cells by repeated centrifugations (50 × g for 3 min) and washing with the same medium. A single-cell suspension was obtained by filtration through 150- and 60-μm nylon mesh. The viability of the cell suspension, as assessed by the exclusion of trypan blue was 90% or higher.

Hepatocytes in suspension (5 × 10^6 cells/ml) were incubated at 37°C in Leibovitz L15 medium. The pH was maintained at 7.4 by passing warm and humidified 95% O2-5% CO2 over the cell suspension. The hepatocyte suspension was stirred throughout the incubation by a Teflon paddle as previously described (17).

The cell culture technique was similar to that described by other

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4 The abbreviation used is: HPLC, high-performance liquid chromatography.

833
EXCRETION AND METABOLISM OF MITOXANTRONE IN RABBITS

authors (19, 20). Hepatocytes, resuspended in Ham's F-12 medium (0.85–1.0 × 10⁶ cells/1.5 ml of medium) supplemented by 10% fetal calf serum, were inoculated in 6-well plastic dishes (35 mm diameter). At the end of a 12-h exposure period, during which cells attached to the plastic dishes, the medium and the dead cells were removed. The hepatocytes were then incubated in serum-free Ham's F-12 medium in the presence of various mitoxantrone concentrations. Extracellular media were recovered at the time points indicated. The monolayers were rinsed twice with phosphate buffered saline (pH 7.4) and removed from the dishes by scraping into the same buffer. Both intra- and extracellular compartments were analyzed for total radioactivity by radioactivity counting and then by HPLC for quantification of the drug and its metabolites (14).

Sample Collection. Immediately before, and at various times after i.v. injection of the radiolabeled drug (every 1–2 min during the first hour, and every 20 min up to the sixth hour), bile samples were directly collected in disposable tubes at 4°C. These samples were carefully protected from light and kept frozen at −20°C until analysis, which was performed not later than 24 h after collection.

Urine was continuously collected and total diuresis was recorded at regular intervals: samples were kept frozen at −20°C in tubes protected from light until HPLC analysis. Bile and urine samples were analyzed by HPLC for metabolite quantification without further processing.

Analytical Method. Analyses of both biological fluids and cellular media were performed with a Hewlett-Packard 1040B gradient liquid chromatograph equipped with a 10-μm particle size C18 Bondapak column (30 cm × 3.9 mm; Waters Millipore S.A.). Elution was carried out at 1.0 ml/min and absorbance was recorded at 254 nm. The mobile phase consisted of formate buffer (pH 4.0; 1.6 mM; solvent A) and acetonitrile/water (48/52; v/v; solvent B) (14, 21). The solvent programmer was set to deliver 45% to 60% of solvent B along a 15-min linear gradient. Eluent from the column was analyzed by a radioactive flow detector (Radiomatic Instruments). Under these HPLC conditions, mitoxantrone was baseline-separated from its various metabolites. Metabolites were identified according to their retention times relative to their standards.

RESULTS

Biliary and Urinary Excretions of Mitoxantrone and Its Metabolites. The biliary excretion of mitoxantrone and of its carboxylic acid derivatives was studied over 6 h following i.v. injection of increasing doses of mitoxantrone, respectively 0.04, 0.20, and 1.00 mg/kg.

Fig. 1 illustrates the kinetics of total radiolabel in bile as a function of time for each dosage regimen. Excretion of radiolabel was very rapid: the time required to reach the peak concentration ranged from 9 to 18 min. The maximal biliary concentrations of total radiolabel were 2.54 ± 0.91, 13.16 ± 2.91, and 74.19 ± 24.41 μg/ml for the different doses administered.

The quantification of unchanged drug and of its different metabolites was investigated after HPLC analysis of each bile sample. A typical chromatogram of mitoxantrone and its metabolites in bile of rabbit is shown in Fig. 24. Biliary excretion data is shown in Table 1. In the first 6 h of collection, following i.v. injection of 0.04, 0.20, and 1.00 mg/kg [14C]mitoxantrone, the total amount of unchanged drug and metabolites excreted in the bile, amounted to 29.5 ± 9.3% (n = 3), 27.6 ± 7.9%, and 28.3 ± 3.8% of total administered drug, respectively. Mitoxantrone metabolites, and in particular the monocarboxylic acid derivative, were present in appreciable amounts (Table 1). Another polar derivative was observed despite the mono- and the dicarboxylic acid derivatives which were identified by coelution with standard metabolites under our chromatographic conditions. Its structure remained unidentified since only very small amounts of this latter compound were accumulated in the bile.

The kinetics of biliary elimination for mitoxantrone and each of its metabolites were further investigated after HPLC analysis of each bile sample. Fig. 3 illustrates the patterns of mitoxantrone and its mono- and dicarboxylic acid derivatives obtained after the i.v. injection of 0.20 mg [14C]mitoxantrone/kg in bile-duct cannulated rabbits. Mitoxantrone and drug-related materials (mono- and dicarboxylic acid derivatives) achieved a maximum biliary concentration of 9.2, 1.7, and 0.2 μg/ml, respectively, during the first 30 min of collection. Their levels then decreased very rapidly to reach undetectable values after the 6th hour. In Table 2 are reported the terminal half-life values at the elimination phase for mitoxantrone and its mono- and dicarboxylic acid derivatives for each dosage regimen.

The urinary excretion of mitoxantrone and its metabolites was also studied over the same period of time. Urinary excretion data is given in Table 1. The total amount of unchanged mitoxantrone and its different metabolites excreted in the urine in the first six hours after i.v. injection of 0.04, 0.20, and 1.00 mg/kg [14C]mitoxantrone accounted for 7.3 ± 0.2% (n = 3), 7.1 ± 4.6%, and 6.0 ± 1.5% of the injected dose, respectively. The total amount of metabolites represented only a very low percentage of excreted drug. A typical chromatogram of mitoxantrone and its metabolites in rabbit urine is shown in Fig. 2B.

Metabolism of Mitoxantrone by Rabbit Hepatocytes. The accumulation and metabolism of mitoxantrone were first studied in freshly isolated rabbit hepatocytes in suspension. Hepatocytes were incubated over 1 h with increasing [14C]mitoxantrone concentrations and, respectively, 1.0, 10.0, and 100.0 μM. Under these experimental conditions, radiolabeled drug was rapidly and intensively accumulated within the hepatocytes with a transmembrane chemical gradient (intra- over extracellular concentration) of approximately 200 for each drug concentration studied, demonstrating that transport was not saturated.
EXCRETION AND METABOLISM OF MITOXANTRONE IN RABBITS

Fig. 2. HPLC chromatograms of mitoxantrone and its different metabolites obtained under various conditions. A, bile sample after i.v. injection of 1 mg/kg [¹⁴C]mitoxantrone; B, urine sample after i.v. injection of 1 mg/kg [¹⁴C]mitoxantrone; C, extracellular medium analyzed after a 24-h incubation of primary culture of rabbit hepatocytes with [¹⁴C]mitoxantrone.

Table 1 Biliary and urinary excretions of mitoxantrone and its various metabolites following i.v. injection of [¹⁴C]mitoxantrone (n = 3)

<table>
<thead>
<tr>
<th>Injected dose (mg/kg)</th>
<th>0.04</th>
<th>0.20</th>
<th>1.00</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bile</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mitoxantrone</td>
<td>7.1±1.6*</td>
<td>40.5±13.5</td>
<td>204.2±47</td>
</tr>
<tr>
<td>Mono-COOH</td>
<td>3.4±1.5</td>
<td>12.3±4.0</td>
<td>55.4±11.3</td>
</tr>
<tr>
<td>Di-COOH</td>
<td>0.6±0.6</td>
<td>1.1±0.6</td>
<td>12.4±6.6</td>
</tr>
<tr>
<td>Polars</td>
<td>0.4±0.5</td>
<td>0.2±0.5</td>
<td>10.7±3.4</td>
</tr>
<tr>
<td>Urae</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mitoxantrone</td>
<td>2.5±0.9*</td>
<td>11.3±10.5</td>
<td>44.8±14.5</td>
</tr>
<tr>
<td>Mono-COOH</td>
<td>0.2±0.1</td>
<td>1.5±2.0</td>
<td>6.0±1.8</td>
</tr>
<tr>
<td>Di-COOH</td>
<td>0.1±0.05</td>
<td>1.3±2.2</td>
<td>4.5±0.9</td>
</tr>
<tr>
<td>Polars</td>
<td>0.1±0.05</td>
<td>0.1±0.3</td>
<td>4.7±1.9</td>
</tr>
</tbody>
</table>

* Results are expressed in µg/kg of body weight.

Table 2 Half-life values for mitoxantrone and its metabolites following i.v. injection of [¹⁴C]mitoxantrone

<table>
<thead>
<tr>
<th>Injected dose (mg/kg)</th>
<th>0.04</th>
<th>0.20</th>
<th>1.00</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mitoxantrone</td>
<td>1.3±0.8*</td>
<td>1.7±0.1</td>
<td>1.3±1.1</td>
</tr>
<tr>
<td>Mono-COOH</td>
<td>1.1±0.2</td>
<td>1.4±0.2</td>
<td>1.5±0.1</td>
</tr>
<tr>
<td>Di-COOH</td>
<td>0.8±0.1</td>
<td>2.0±0.3</td>
<td>1.4±0.2</td>
</tr>
</tbody>
</table>

* Half-life values are expressed in hours.

over this concentration range. However under these experimental conditions only 10% of the initial drug was metabolized, mainly to the monocarboxylic acid derivative. So as to enable mitoxantrone metabolism to be more fully investigated, studies were undertaken using primary cultures of rabbit hepatocytes.

The metabolic pattern of mitoxantrone was evaluated in both intra- and extracellular compartments following incubation of the hepatocytes over 48 h with 5 µM [¹⁴C]mitoxantrone. Unchanged mitoxantrone disappeared rapidly to attain an extracellular concentration of 0.70±0.18 µM after 48 h (Fig. 4). The rapid decrease of extracellular mitoxantrone is attributable to its large-scale accumulation within the cells and its subsequent metabolism. Three metabolites appeared in the extracellular compartment. Two of them were identified (Fig. 2C) as the mono- and dicarboxylic acid derivatives of mitoxantrone on the basis of their retention times relative to the standard metabolites. The third metabolite corresponds to a very polar derivative since its retention time under these HPLC conditions was identical to that of void volume. Although its identity remains unknown, it was not a degradative product generated during the incubation period. Indeed, when [¹⁴C]mitoxantrone was incubated for 48 h in hepatocyte-free medium, and the medium was analyzed by HPLC, neither metabolites nor degradative compounds were generated.

The monocarboxylic acid derivative first appeared in the extracellular compartment, i.e., 30 min after mitoxantrone incubation. Its level increased over the entire period of observation up to 1.28±0.50 µM. The dicarboxylic acid derivative appeared later. Its level remained lower but similar to that of polar derivatives (0.49±0.18 µM and 0.39±0.14 µM, respectively). After a 48-h incubation period, 75.0±5.0% of extracellular radiolabel was accounted for by metabolites among which the monocarboxylic acid was the main derivative.
The intracellular compartment was also analyzed for its metabolite content. Results (expressed in nmol/10^6 cells) are shown in Table 3.

The intracellular content was analyzed following the incubation of hepatocytes in primary culture with increasing [14C]mitoxantrone concentrations and for various exposure times. Unchanged mitoxantrone represented the main intracellular form at each time point studied, while under the same incubation conditions, the monocarboxylic acid derivative represented the main extracellular form (Table 3).

Metabolism of mitoxantrone was also investigated after a 48-h exposure of hepatocytes in primary culture to increasing [14C]mitoxantrone concentrations ranging between 1 and 20 μM. Fig. 5 illustrates the 24-h extracellular concentrations of unchanged mitoxantrone and of its various metabolites, as a function of the initial extracellular mitoxantrone concentration. Over this range of concentration, accumulation of both the mono- and dicarboxylic acid derivatives remained linear, while the extracellular concentration of the polar derivative(s) achieved plateau values for initial mitoxantrone concentrations ranging between 10 and 20 μM.

The extracellular concentration of unchanged mitoxantrone increased as a linear function of initial extracellular mitoxantrone concentrations of up to 15 μM.

<table>
<thead>
<tr>
<th>Exposure time (h)</th>
<th>Drug concentration†</th>
<th>Mitoxantrone</th>
<th>mono-COOH</th>
<th>di-COOH</th>
<th>Polar</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 μM</td>
<td></td>
<td>0.22 ± 0.03</td>
<td>0.04 ± 0.04</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>0.24 ± 0.01</td>
<td>0.06 ± 0.01</td>
<td>0.01 ± 0.01</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>0.19 ± 0.03</td>
<td>0.06 ± 0.02</td>
<td>0.01 ± 0.01</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>12</td>
<td>0.16 ± 0.02</td>
<td>0.06 ± 0.01</td>
<td>0.02 ± 0.02</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>20 μM</td>
<td></td>
<td>1.19 ± 0.08</td>
<td>0.14 ± 0.04</td>
<td>0.04 ± 0.03</td>
<td>0.05 ± 0.05</td>
</tr>
<tr>
<td>2</td>
<td>1.10 ± 0.10</td>
<td>0.17 ± 0.03</td>
<td>0.07 ± 0.06</td>
<td>0.12 ± 0.05</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>1.02 ± 0.04</td>
<td>0.21 ± 0.04</td>
<td>0.08 ± 0.02</td>
<td>0.09 ± 0.04</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>0.96 ± 0.12</td>
<td>0.33 ± 0.08</td>
<td>0.11 ± 0.02</td>
<td>0.11 ± 0.05</td>
<td></td>
</tr>
<tr>
<td>20 μM</td>
<td></td>
<td>4.72 ± 0.28</td>
<td>0.51 ± 0.16</td>
<td>0.07 ± 0.12</td>
<td>0.36 ± 0.14</td>
</tr>
<tr>
<td>2</td>
<td>5.34 ± 0.37</td>
<td>0.73 ± 0.09</td>
<td>0.17 ± 0.16</td>
<td>0.19 ± 0.17</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>4.52 ± 0.27</td>
<td>0.93 ± 0.17</td>
<td>0.31 ± 0.10</td>
<td>0.21 ± 0.20</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>5.27 ± 0.68</td>
<td>1.87 ± 0.56</td>
<td>0.31 ± 0.27</td>
<td>0.15 ± 0.27</td>
<td></td>
</tr>
</tbody>
</table>

† Results are expressed in nmol/10^6 cells.

FIG. 5. Metabolism of mitoxantrone as a function of extracellular mitoxantrone concentration. Freshly isolated rabbit hepatocytes in primary culture were incubated with increasing [14C]mitoxantrone concentrations. After a 48-h exposure, extracellular compartment was recovered and analyzed by HPLC. Data are the average of two or the mean of three different experiments.

DISCUSSION

This report demonstrates that the liver plays an important role in the pharmacokinetic behavior of mitoxantrone.

This important conclusion is based upon the following observations.

First in rabbits, mitoxantrone and its metabolites were rapidly and intensively excreted via the bile route. Over a 6-h period of observation, 25 to 30% of the administered drug was eliminated in bile. Drug-related material, and the monocarboxylic acid derivative in particular, represented approximately 30% of the excreted dose. Urinary excretion of mitoxantrone and its metabolites was, to the contrary, low, amounting to less than 6 to 8% of the dose during a 6-h observation period. Both the biliary and urinary excretions of mitoxantrone and its metabolites remained linear over a range of doses routinely used in clinic, e.g., 0.04 to 1.0 mg/kg. The intense biliary excretion of drug shown in rabbit was in agreement with previous reports on studies with rats (8–10), dogs (7), and humans (11, 12). The present study demonstrates that metabolites, and most importantly the monocarboxylic acid derivative, represent a high percentage of the excreted material. Ehninger et al. (8), using the isolated perfused rat liver model, also reported the presence of three mitoxantrone metabolites. The major metabolite, the most polar, accounted for 80% of the excreted material. On the basis of the respective chromatographic conditions, this metabolite would not correspond to the mono- and dicarboxylic acid derivatives we identified in rabbits, but rather to our polar metabolite. This (these) latter metabolite(s) would appear to correspond to a conjugate derivative with glucuronic acid or glutathione (13). This suggests large interspecies differences in metabolic patterns between rat and rabbit.

Second, using freshly isolated rabbit hepatocytes in primary culture we demonstrated that mitoxantrone was intensively metabolized to mono- and dicarboxylic acid derivatives. Another metabolite was also recovered in the extracellular compartment but its level remained low over the entire period of observation. Although this latter remained unidentified it may, in accordance with its characteristics determined under our analytical conditions, correspond to a conjugate derivative. Metabolites synthesized in the intracellular medium rapidly effluxed in the extracellular compartment, representing approximately 70% of the extracellular material after a 48-h exposure to mitoxantrone. The metabolites identified in the extracellular medium following exposure of rabbit hepatocytes in primary culture to mitoxantrone, are qualitatively and quantitatively similar to those observed in bile. Previous reports from our laboratory (14) have shown that mitoxantrone is also intensively metabolized by both rat and human hepatocytes in primary culture. While mono- and dicarboxylic acid derivatives were the main derivatives recovered after exposure of human hepatocytes to mitoxantrone, the main derivative observed in rats was a polar one perhaps corresponding to the conjugate derivative(s) observed by Ehninger (8) and Wolf (13). From our studies in rat (14), rabbits, and humans (14), it can be assumed that the rabbit is more closely related to humans than the rat at least as far as the metabolic pattern is concerned. The appearance and the accumulation of the mono- and dicarboxylic acid derivatives increased in a concentration-dependent manner, when hepatocytes in primary culture were exposed to mitoxantrone concentrations ranging between 1 and 20 μM. This concentration range corresponds to the medium and high plasma levels routinely encountered in clinic (21). The approximate linearity observed for intra- and extracellular accumulation and metabolism has...
also been observed by others (22, 23). Burns et al. (22) showed in L-1210 leukemia cells that passive diffusion is the mechanism of mitoxantrone uptake, since the uptake remained linear over a broad concentration range, temperature-dependence was limited and transport was not impeded by a wide range of metabolic inhibitors.

This first detailed analysis of mitoxantrone excretion and metabolism in rabbit, demonstrates the important role played by the liver in the pharmacokinetic behavior of this new antitumor drug. Thus, liver dysfunction may result in decreased clearance of mitoxantrone. Therefore, and in agreement with other authors (24–26), drug dosages should be reduced in patients with severe liver dysfunction.

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