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The measurement of haloperidol and reduced haloperidol in hair as an index of dosage history

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1 We report a method for measuring the concentrations of haloperidol (HL) and its major active metabolite, reduced haloperidol (RHL), in human scalp hair.
2 Hair samples were obtained from 59 patients who had been taking HL at fixed daily doses for more than 4 months and whose compliance was good. A morning pre-dose plasma sample was also obtained from 48 of these patients.
3 The concentrations of HL and RHL in hair (ng mg^{-1} hair) correlated significantly both with the daily dose ($\mu g\ kg^{-1}$ body weight) of HL ($r = 0.682$, $P < 0.001$ for HL and $r = 0.813$, $P < 0.001$ for RHL, $n = 59$) and with the trough concentration (ng ml^{-1}) of the corresponding compound in plasma at steady state ($r = 0.558$, $P < 0.001$ for HL and $r = 0.563$, $P < 0.001$ for RHL, $n = 48$). The correlation coefficients were slightly higher using the sum of the concentrations of both substances in hair ($r = 0.829$ for the correlation with daily dose and $r = 0.609$ for that with trough concentration).
4 Hair from other patients, in whom the dosage of HL had been changed within a few months prior to sampling, was sectioned into 1 cm-long portions successively from the roots and the concentrations of both compounds in each portion were measured. Assuming a growth rate of 1–1.5 cm/month, a history of individual dosage could be deduced in all patients from the distribution of the drug and metabolite along the single hair length.
5 These results show that both HL and RHL are excreted into human scalp hair to a similar degree, that the measurement of both substances may provide a slightly better index of individual dosage history of HL than the measurement of the individual compounds and that human scalp hair might serve as a useful sample for monitoring individual dosage history.

Keywords scalp hair haloperidol reduced haloperidol dosage history

Introduction

Information on drug concentration in biological samples is often useful when adjusting individual dosage (Dahl, 1986). Usually, drug concentrations in body fluids such as blood, saliva and urine are used for this purpose. However, these concentrations may reflect only dosage over several days prior to the sampling of the specimen. To assess compliance over longer periods it would be an advantage to sample a readily accessible tissue which provides a more permanent marker of drug intake. Human scalp hair is often used to monitor the ingestion of toxic substances such as heavy metals (Kopito *et al.*, 1969; Weiss *et al.*, 1972). Thus, it has been used to estimate the body burden of mercury in poisoned patients (Taubaki, 1971; Al-Shahristani

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& Al-Haddad, 1973; Jervis & Tiefenbach, 1971) and as an epidemiological monitor of exposure to environmental metals such as lead and arsenic (Schroeder & Nason, 1969). These studies showed that hair captures the history of individual exposure to metals in relation to the distribution of the concentration of the substance along the hair length (Chattopadhyay *et al.*, 1977).

We have been interested in the use of human scalp hair to monitor the dosage history of drugs and have shown that hair contains haloperidol corresponding to the given dose, thereby suggesting the potential usefulness of hair analysis in therapeutic drug monitoring (Uematsu *et al.*, 1989). Haloperidol is one of the most widely used psychotropic drugs and may be administered for a long period of time. Its major metabolite, reduced haloperidol, may contribute to the effects of the parent drug.

Therefore, in the present study we have developed a method for measuring haloperidol and reduced haloperidol simultaneously in scalp hair and show the potential utility of measuring both compounds as an index of dosing history and compliance.

Methods

Subjects

The subjects of the study were inpatients in a psychiatric hospital who were controlled on maintenance doses of haloperidol given three times per day and whose compliance was good. Pre-dose blood (5ml) was collected in heparinized tubes at 07.30 h (about 13 h after the last dose) from each patient as part of routine therapeutic monitoring of haloperidol. On the same day the patients provided samples of hair either by combing out loose stands or by cutting a few strands near to the roots. The patients gave their informed consents to these procedures. The patients comprised 25 men and 34 women aged 22 to 77 years old with weights ranging from 33 to 74 kg. They were given fixed daily doses of haloperidol in granule form (3 to 30 mg day^{-1} of Serenace, Dainppon Pharmac. Co., Halosten, Shionogi Pharmac. Co., or Linton, Yoshitomi Pharmac Co., Japan) for more than 4 months. In a separate experiment hairs were collected in the same way from each of five patients (four men, one woman), in whom the dosage of haloperidol had been changed within a few months prior to sampling.

The protocol of the study was approved by a local ethics committee.

Preparation of samples

All glassware was siliconized to prevent adsorption of haloperidol. A 1 to 2-cm length of hair nearest to the root was obtained from a single strand. This was washed successively with a 0.1% w/v solution of sodium dodecyl sulphate (SDS) and distilled water. The hair was blotted between two paper towels and allowed to dry in air. It was then weighed, cut into pieces of about 2 mm long and dissolved in 1 ml of 2N NaOH by heating at 80°C for 30 min. To 0.5 ml of this sample or to 0.5 ml plasma, NaOH (0.5 ml 2N) and n-hexane (5 ml) containing 1.5% v/v isoamylalcohol were added and the mixture was shaken for 15 min. After centrifugation at 3000 *g* for 2 min, 1 ml of the separated organic layer was transferred to another tube. The solvent was evaporated at 50°C. Methanol (0.1 ml) was added to the residue, the solution was vortexed briefly and then injected into an h.p.l.c. system. For the radioimmunoassay of haloperidol 0.05 ml of methanol and 0.7 ml of 0.075 M phosphate buffer (pH 7.4) containing 1% w/v bovine serum albumin were added to the residue.

Assay procedures

Haloperidol and reduced haloperidol were measured simultaneously by h.p.l.c. with a coulometric detector according to the methods of Korpi *et al.* (1983) and Midha *et al.* (1988) with slight modifications. A Shimadzu LC–6A (Kyoto, Japan) was used together with a Coulochem detector, a high-sensitivity cell and a guard cell (5100A, 5020 and 5100, ESA, Bedford, MA, U.S.A.). The column was TSK Gel 80–TM ODS (150 × 4.6 mm i.d.). The mobile phase was a mixture of 50 mM potassium phosphate buffer (pH 6.8), CH_3CN and CH_3OH (3:2:1, v/v). Bromperidol was used as the internal standard. The sample was eluted at a flow rate of 0.8 ml min^{-1}. The injection volume was 25–50 μl. Each measurement was made in duplicate. Haloperidol together with reduced haloperidol and bromperidol were supplied by the Dainippon Pharmac. Co. (Osaka, Japan) and Yoshitomi Pharmac. Co. (Osaka, Japan), respectively.

Assay linearity and precision

The correlation coefficients of calibration curves for measuring haloperidol (0.5–4.0 ng ml^{-1}) and reduced haloperidol (0.5–4.0 ng ml^{-1}) were 0.997 ($P < 0.001$) and 0.998 ($P < 0.001$), respectively. The coefficients of variation at concentrations of 0.5, 1.0, 2.0 and 4.0 ng ml^{-1} were 10.2,

Table 1 Variability in the measurement of haloperidol and reduced haloperidol in hair

	Haloperidol			*Reduced haloperidol*		
Subject	*Mean (ng mg^{-1})*	*s.d.*	*CV (%)*	*Mean (ng mg^{-1})*	*s.d.*	*CV (%)*
1	37.1	6.2	16.7	20.7	6.2	29.9
2	14.8	3.7	24.9	21.2	4.0	18.8
3	14.5	2.1	14.1	16.1	3.2	19.9
4	50.7	8.4	16.7	44.9	4.8	10.6
5	24.8	2.1	8.3	29.8	6.8	22.8
6	61.9	7.2	11.7	68.6	7.0	10.2
7	14.8	1.3	8.7	25.0	2.8	11.2
8	33.1	4.7	14.5	25.4	2.3	9.3
		Mean	14.5		Mean	16.6
		s.d.	±4.9		s.d.	±6.9

The concentrations in hair of haloperidol and reduced haloperidol were measured by h.p.l.c. in eight patients (Subject 1–8) using five different strands of hair obtained from each patient. CV: coefficient of variation.

7.9, 8.8 and 13.0% for haloperidol and 4.2, 10.1, 10.7 and 9.4% for reduced haloperidol, respectively. Therefore, the measurements were performed within the range of 0.5–4.0 ng ml^{-1} in final concentrations of both substances.

The intraindividual variabilities of concentrations in hair of haloperidol and reduced haloperidol were determined in eight patients by assay of five different strands of hair obtained from the same patient. The results are shown in Table 1.

The influence of extraction method on the measurement of haloperidol and reduced haloperidol in hair

Each 1 to 2 cm-length of hair nearest to the root obtained from three hair strands of the same patients was washed with distilled water. They were then placed either in 1 ml of 0.1% SDS solution for 48 h with sonication for a total of 24 h, in 1 ml of methanol for 48 h with sonication in the same way, or dissolved completely in 1 ml of 2N NaOH with heating at 80°C for 30 min. Both components in each of the three solutions were measured. The methanol solution was injected directly into the h.p.l.c. after filtration through a millipore filter (0.22 μm pore size), while the compounds in either NaOH solution or SDS were extracted with n-hexane. The recovery of both compounds dissolved in the solution containing SDS was much less (< 10%) than in the other two solutions. The recoveries in the methanol and NaOH solutions were similar. However, interfering peaks were sometimes apparent in chromatograms from the methanolic extract. Therefore, in this study we dissolved the hair in 2N NaOH solution and both substances were extracted with n-hexane.

Comparison of h.p.l.c. with radioimmunoassay for haloperidol measurement

Haloperidol was also measured by radioimmunoassay (Poland & Rubin, 1981; Rimon *et al.*, 1981; Smith *et al.*, 1984; Wurzburger *et al.*, 1981). Haloperidol antiserum from an immunized rabbit and [^{3}]H-haloperidol (labelled at the 3-position of the 4-chlorophenyl moiety) with a specific activity of 12.5 Ci mmol^{-1} (I.R.E., Belgium) were supplied by the Dainippon Pharmac. Co., Ltd (Osaka, Japan) (Suzuki *et al.*, 1980). The dilution of antiserum which exhibited 50% binding to the labelled antigen was 1:4500, showing an appropriately high affinity for haloperidol. The procedures for measuring haloperidol in hair with the radioimmunoassay are described in detail elsewhere (Uematsu *et al.*, 1989). Cross-reactivities of haloperidol with its major metabolites have been reported to be less than 0.1% (Suzuki *et al.*, 1980). Haloperidol was prepared in methanol at a concentration of 4 ng ml^{-1} and diluted to 0.5 ng ml^{-1}. Three aliquots of each diluted solution were measured in duplicate both with h.p.l.c. (y) and with radioimmunoassay (x). The results showed a good agreement between the two methods [$y = 0.96\,x + 0.058$, $r = 0.994$ ($P < 0.001$)].

Results

Haloperidol was not detected in hair from control subject who had never been administered the drug. It was found in samples from all patients who had been administered the drug. Reduced haloperidol were also detected in hair from all patients except one, whose pre-dose plasma contained both haloperidol and reduced haloperidol. The concentration ranged from 3.44 to 208.11 ng mg^{-1} hair for haloperidol and from 4.11 to 106.52 ng mg^{-1} hair for reduced haloperidol. The concentrations of haloperidol and reduced haloperidol each correlated significantly both with the daily dose of haloperidol and with the trough concentration of the corresponding compound in plasma at steady state (Figures 1 and 2). The correlation coefficients obtained using the summed concentration of haloperidol and reduced haloperidol were slightly higher (Figures 1 and 2, lowest panels). The trough concentration of haloperidol in plasma at steady-state did not correlate significantly with the daily dose, while that of reduced haloperidol

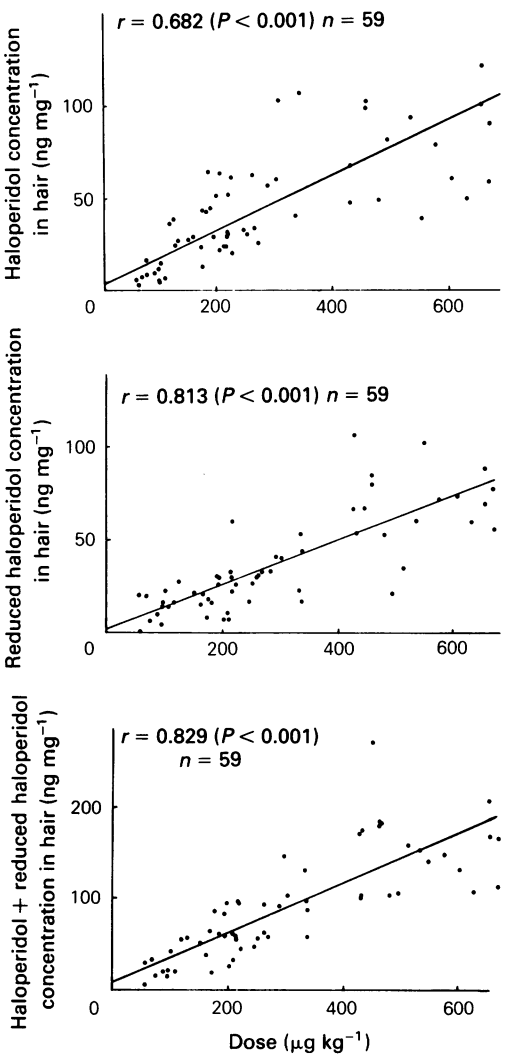

Figure 1 Relationships between the daily dose of haloperidol and concentration in hair of haloperidol (upper panel: y = 0.15x + 6.59), reduced haloperidol (middle panel: y = 0.12x + 2.64) and their sum (lower panel: y = 0.26x + 9.23) in psychiatric patients.

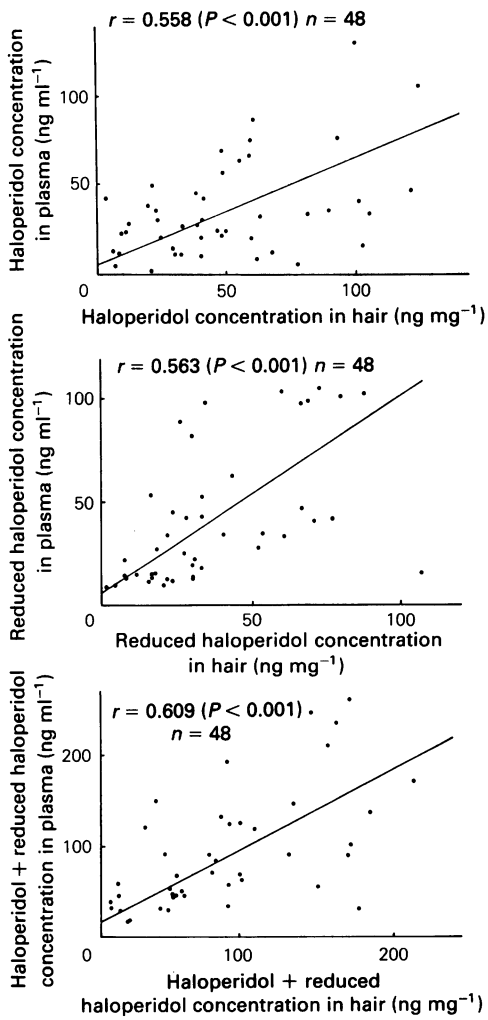

Figure 2 Relationships between concentrations in hair and plasma of haloperidol (upper panel: y = 0.48x + 13.66), reduced haloperidol (middle panel: y = 1.16x + 22.48) and their sum (lower panel: y = 0.74x + 22.48) in psychiatric patients.

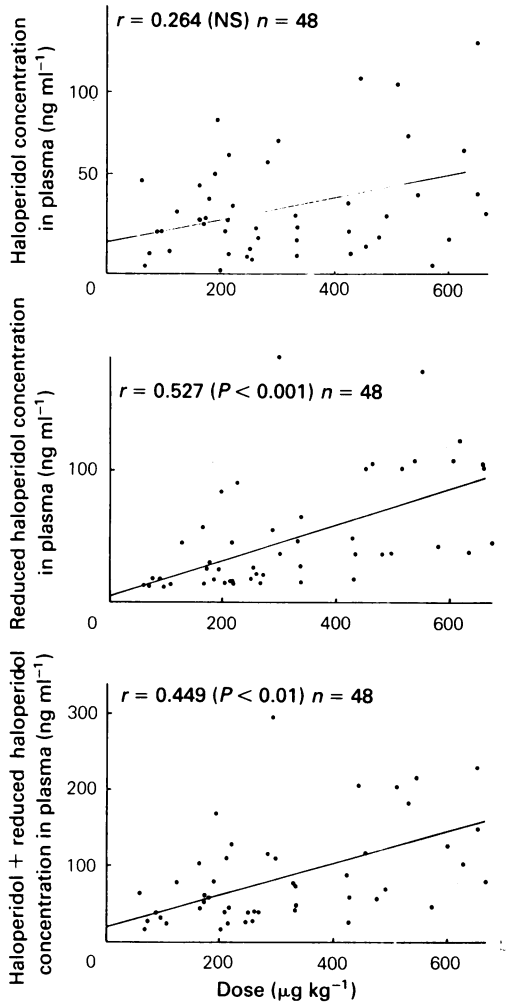

Figure 3 Relationships between daily dose of haloperidol and concentration in plasma of haloperidol (upper panel; NS: not significant), reduced haloperidol (middle panel: y = 0.16x + 24.79) and their sum (lower panel: y = 0.17x + 74.11) in psychiatric patients.

and the summed value did (Figure 3). The ratios of hair concentration (ng mg^{-1}) to trough plasma concentration at steady state (ng ml^{-1}) were 1.17 ± 4.49 and 0.88 ± 1.89 (mean s.d.) for haloperidol and reduced haloperidol, respectively.

The distribution of haloperidol and reduced haloperidol along a single strand of hair was examined in five patients in whom the dosage of haloperidol had been decreased successively or discontinued a few months before sampling. Three representative results are shown in Figure 4. In all five patients, the times at which dosage

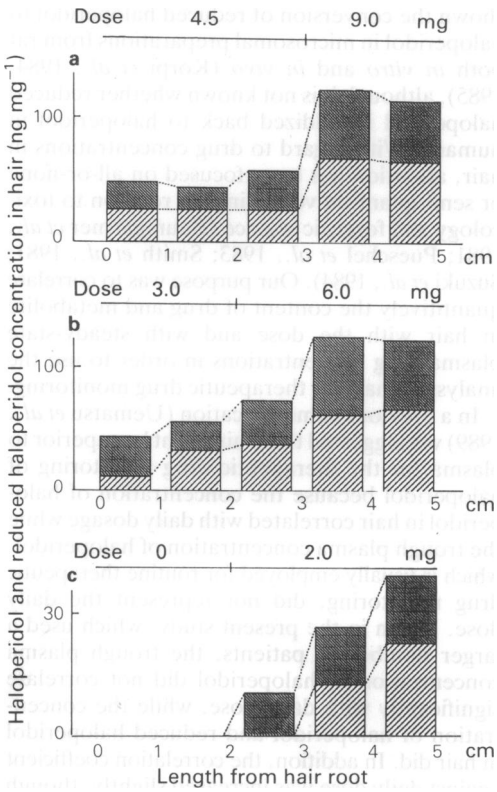

Figure 4 Distribution of haloperidol (▨) and reduced haloperidol (■) concentrations along the length of a single strand of hair in relation to dosage history of haloperidol. Individual dosage history of haloperidol is depicted in the bar above each panel assuming a hair growth of 1 cm/month.

changed were indicated by abrupt changes in the concentrations of both haloperidol and reduced haloperidol.

Discussion

Our findings show that hair contains both haloperidol and its major metabolite, reduced haloperidol, in correspondence with the dose of haloperidol. Simultaneous measurement of both compounds is indicated for therapeutic drug monitoring of haloperidol because it has been suggested that high concentrations of reduced haloperidol may be associated with a poor therapeutic response (Altamura *et al.*, 1987; Ereshefsky *et al.*, 1984). Experiments in which reduced haloperidol was applied directly to rat brain neurons showed no evidence of neuroleptic-like antagonism in either dopaminergic or adrenergic systems (Kirch *et al.*, 1985). Other studies have

shown the conversion of reduced haloperidol to haloperidol in microsomal preparations from rat both *in vitro* and *in vivo* (Korpi *et al.*, 1984, 1985), although it is not known whether reduced haloperidol is oxidized back to haloperidol in humans. With regard to drug concentrations in hair, attention has been focused on all-or-none or semi-quantitative findings in relation to toxicology and forensic science (Baumgartner *et al.*, 1981; Pueschel *et al.*, 1983; Smith *et al.*, 1981; Suzuki *et al.*, 1984). Our purpose was to correlate quantitively the content of drug and metabolite in hair with the dose and with steady-state plasma drug concentrations in order to use the analysis of hair for therapeutic drug monitoring.

In a previous communication (Uematsu *et al.*, 1989) we suggested that hair might be superior to plasma for the therapeutic drug monitoring of haloperidol because the concentration of haloperidol in hair correlated with daily dosage while the trough plasma concentration of haloperidol, which is usually employed for routine therapeutic drug monitoring, did not represent the daily dose. Again in the present study, which used a larger number of patients, the trough plasma concentration of haloperidol did not correlate significantly with daily dose, while the concentration of haloperidol and reduced haloperidol in hair did. In addition, the correlation coefficient against daily dose was increased slightly, though not significantly, when the sum of both concentrations was used. Furthermore, since hair grows progressively and can incorporate drug in concentrations that vary with blood concentrations, such simultaneous measurements of the content of parent drug and its active metabolite provides a measure of their mean content in the whole body that would otherwise have to be obtained by repeated blood sampling. The ratio of the concentration in hair to trough plasma concentration is slightly, although not significantly, lower for reduced haloperidol than for haloperidol, possibly reflecting its greater hydrophilicity. As can be expected from the time profiles of both substances in plasma after oral administration of haloperidol, which show that the fluctuations of reduced haloperidol between successive administrations are less than those of parent drug (Midha *et al.*, 1988), simultaneous measurement of haloperidol and reduced haloperidol in plasma or hair might provide a better index of the daily doses of haloperidol than single measurements of trough plasma haloperidol.

In this study we used only a single strand of hair for measuring concentrations of both compounds in hair and correlated these concentrations with haloperidol dosage or those in plasma from the same individual. However, we have also assessed the intraindividual variabilities of haloperidol and reduced haloperidol concentrations in hair by measuring the content of several different strands of hair obtained from the same patient. The intraindividual variabilities were 8.3–24.9% for haloperidol 9.3–29.9% for reduced haloperidol when expressed as CV%. This rather large intraindividual variance will, therefore, contribute to the interindividual variance shown in Figure 1 (lowest panel). It is well known that human scalp hair has its own growth cycle of about 2 to 8 years or more (Kligman, 1961; Montagna & Parakkal, 1974), i.e., 2 to 8 years or more of anagen (growing stage), a few weeks of catagen (intermediate stage) and a few months of telogen (resting stage). It has been reported that about 85% of total hair in Japanese is in the growing stage (Takashima, 1987). Therefore, in collecting only one strand of hair, the possibility of it being in the resting stage could be as large as 15%. Concerning the compliance of our patients, the ingestion of drugs was usually supervised by the nursing staff. However, we could not exclude the possibility of poor compliance. Thus, two uncertainties, namely that regarding the stage of hair growth and the possibility of incomplete compliance may also have contributed to the rather large intra- and interindividual variances observed in the data. To minimize variance due to uncertainty about the stage of hair growth we recommend the assay of ten or more strands of hair.

Since it is possible to measure both compounds simultaneously in a 1 to 2 cm segment of a single hair strand, this allows an analysis of the month-by-month dosage history imprinted in that strand (Figure 4) because a 1 to 1.5 cm-length represents the hair growth in 1 month (Barman *et al.*, 1965; Griffiths & Reshad., 1983; Montagna & Parakkal, 1974). For this kind of analysis the distribution of relative concentration along the hair length would be sufficient rather than a knowledge of absolute concentrations. This obviates the problem of large intraindividual variability among different strands of hair. The effect of placing specimens in a strong detergent (SDS) for a long period of time on the content of haloperidol and reduced haloperidol was negligible, indicating that the amounts of the compounds attached superficially to hair through excretion into sebaceous material was small. Since hair is an oily tissue with dust adhering to it, the washing technique is critical in the analysis of metals in order to avoid contamination with metals in dust (Chattopadhyay *et al.*, 1977; Ryan *et al.*, 1978). We suggest that washing hair with distilled water and SDS should be sufficient for

the analysis of drug content in hair. In conclusion, we have shown the potential utility of assaying scalp hair to assess the individual dosage history of haloperidol.

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