Stable Isotopes Labeling of Drugs in Pediatric Clinical Pharmacology

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ABBREVIATIONS. SIL, stable isotope labeling; CBT, CO₂ breath test; HPLC, high-pressure liquid chromatography; CAF, caffeine; GH, growth hormone; CBZ, carbamazepine.

Stable isotope labeling (SIL) still has not been used very much in pediatric and perinatal clinical pharmacology. However, this method has numerous advantages. It allows one to determine the concentration of drugs with great sensitivity, thereby allowing quantification in small amounts of biologic samples. It also allows quantification with great specificity, eliminating interference by drug metabolites found in some radioactive tracer methods. SIL is safe because stable isotopes are not radioactive. The only possible toxicity that may be related to an isotope effect is a slowing of biochemical reactions because of the greater mass of the stable isotope. Because of the great difference between deuterium and hydrogen, a significant isotope effect occurs only with deuterium. However, toxicity related to the isotope effect of deuterium can only be produced by very high levels of deuterium (>15% of body water), far higher than the amount of deuterium in a typical tracer dose of drug. SIL also allows noninvasive studies such as the CO₂ breath test (CBT). All of these advantages explain the great potential interest in SIL in pediatric pharmacology. The costs of stable isotopes and limited facilities available for sample analysis are undoubtedly the greatest limitations to their increased use.

SIL is useful in different types of studies such as studies on the fate of drugs (drug metabolic pathways and pharmacokinetics), determination of compliance, and assessment of therapeutic and unwanted effects of drugs.

The use of SIL of drugs in positron emission tomography investigations is not addressed in this article.

STABLE ISOTOPES

Definition

In the periodic table, the elements are ranked according to their atomic number, i.e., the number of protons contained in the nucleus. All elements located at the same place in the table are isotopes of the same family, for example, the family of carbon. All members of the same family are characterized by the same number of protons, but they differ by the number of neutrons.

The structure of the nucleus of radioactive isotopes is unstable, and a disintegration occurs with emission of an ionizing radiation. The radioactive isotopes can be identified by the detection of this radiation. On the contrary, the structure of the nucleus of stable isotopes is stable and no disintegration occurs. Stable isotopes contain one or more additional neutrons and therefore are heavier than the normally abundant isotope of the considered atom. Because of this difference in atomic weight, the stable isotopes can be identified and differentiated by mass spectrometry. Some isotopes are naturally occurring, others are manmade. The natural occurrence varies very much from one isotope to another.

SIL

Stable isotopes can be incorporated into a molecule, producing a molecule with a higher molecular weight than that of the unlabeled molecule.

The natural SIL of molecules is proportional to the natural occurrence of the considered stable isotope and yields a low rate of labeling. Artificial SIL allows higher rates of labeling.

Isotopic Effect

When an atom in a chemical radical is replaced by a stable isotope (e.g., hydrogen replaced by deuterium), the mass of the radical is modified and the physical molecular interactions may be modified with kinetic changes on chemical reactions that define the isotopic effect. For example, the replacement of the hydrogen atoms of a methyl group by atoms of deuterium may decrease the rate of demethylation of a chemical compound.

Mass Spectrometry

Mass spectrometry is a technique that allows identification and quantification of compounds labeled with a stable isotope.

Biologic samples to be assayed using mass spectrometry have to undergo an extraction and a separation that is performed most often by gas chromatography and, more recently, by high-pressure liquid chromatography (HPLC).

Separation by gas chromatography is used for volatile compounds and compounds that can be derivatized, i.e., that can be bound to a radical that increases the mass of the fragment. Separation by
HPLC has to be used for thermolabile molecules, large molecules (eg, prostaglandins), and molecules difficult to obtain in a vapor state (eg, glycuron conjugates). The separated fractions are injected in the vapor state into a chamber of ionization. The liquid fractions obtained during HPLC have to be nebulized to be in a vapor state while the sample is dried under a flow of nitrogen. The most common ionization process is achieved by bombardment of the molecules with electrons at 70 electron volts of energy (electron impact ionization) or of ions (chemical ionization). Most of the injected molecules are broken into fragments, and both fragments and unbroken molecules are ionized and accelerated in an electric field. They enter a magnetic field, and the deflection of their path is proportional to their electric charge and inversely proportional to the mass and speed. In the mass spectrum obtained for each fraction of the chromatogram, the ion clusters allow the identification of labeled fragments and unbroken molecules. Ion clusters are characteristic twin peaks of the mass spectrum corresponding to a molecular fragment or to the unbroken molecule (molecular ion) and its corresponding stable isotope-labeled homolog. A computer-reconstructed total ion chromatogram is obtained from the consecutive mass spectra obtained from the same sample.

APPLICATIONS TO PEDIATRIC PHARMACOLOGY

Studies on the Fate of Drugs

Studies on Drug Metabolic Pathways

The isotope cluster technique is a powerful method for the detection and structural identification of drug metabolites. It also is a useful tool for tracing the origin and sequence of the addition of groups to a drug during biotransformation.

N7 Methylation of Theophylline in Neonates

The N7 methylation of theophylline into caffeine (CAF) has been demonstrated in premature neonates by Brazier and colleagues using SIL.3,4 CAF had already been detected in plasma of premature neonates receiving theophylline for treatment and prevention of apnea.5,6–8 Plasma concentrations of CAF correlated with those of theophylline, with variations occurring in parallel. Three hypotheses have been raised to explain how CAF was present in plasma: 1) transferred transplacentally; 2) transferred via human breast milk; or 3) theophylline was transformed, in vivo, into CAF. Indeed, CAF is a methylxanthine, like theophylline, but CAF has an additional methyl group on the N7 position.

To verify the third hypothesis, Brazier and colleagues used theophylline labeled with two stable isotopes, nitrogen 15 on the 1 and 3 positions, carbon 13 on the 2 positions.3,4 Two premature twin infants received theophylline, 3 mg/kg every 8 hours, starting on day 2 for 8 days as a mixture of 46% of the labeled form and 54% of the unlabeled form. Using gas chromatographic mass spectrometry, the investigators showed that in plasma and urine, CAF molecules have the same labeling as the administered theophylline molecules.

The mass spectrum of CAF extracted from the urine showed the molecular ion cluster of CAF, 194 and 197, that corresponds to unlabeled and trilabeled CAF, respectively. The other ion clusters produced by the fragmentation of CAF and theophylline demonstrate that the CAF molecules had the same labeling as the administered theophylline molecules.

The presence of labeled CAF in plasma and urine of infants treated with labeled theophylline confirms the biotransformation of theophylline into CAF via N7 methylation. This metabolic pathway is virtually undetectable in adults.9

CBT

The CBT allows one to study the demethylation and decarboxylation of molecules.

The principle of the CBT is as follows. One or several carbon atoms of an administered molecule is metabolized via a demethylation or a decarboxylation into formaldehyde, formic acid, formyltetrahydrofolate, and CO2. If the molecule is artificially enriched with 13C on the position to be metabolized, the expired gas is enriched with -CO2 proportionately to the drug metabolism. When the carbon atom belongs to a methyl group, the CBT allows a noninvasive measurement of the demethylation of the molecule, as long as the transformation of formaldehyde produced into CO2 is not a limiting step of the production of CO2. It has been shown in rodents that the CBT is an effective method for measuring the activity of the isoenzymes depending on CYP 1A2.10,11

Because it is not easy to measure directly the activity of the enzyme in humans, a correlation between the rate of expired labeled CO2 and an indirect measure of the enzyme activity, such as plasma clearance, has been sought. Such a correlation already has been evidence for aminopyrine12 and CAF13,14 demethylations. This is consistent with the understanding that demethylation explains most of the aminopyrine and CAF clearance.

Maturation of N-Demethylation of CAF in Neonates and Infants

The CBT has been used to study the maturation of N-demethylation of CAF in neonates and infants.15 The study was performed in 12 children, 4 premature neonates and 8 infants (1–19 months old). They received oral CAF citrate solution for treatment and prevention of apnea. The usual morning maintenance dose was substituted by 1,3,7–13C trimethylxanthine.

The expired gas was collected over a 1-minute period using a face mask and a small dead volume two-way valve into a Latex bag. The volume of expired gas was measured with a pneumotachograph connected to a flow transducer. Aliquots were transferred to vacuum-evaluated glass flasks. Five breath samples were collected between two consecutive doses: the day before the administration of labeled CAF (day 1) for endogenous labeled CO2 production and the day after (day 2). They were collected just before the dose and 2, 3, and 6 hours after this dose and before the next scheduled dose. Blood samples were drawn by heel prick after each breath sample
collection on day 2. Urine samples were collected on day 2.

The \(^{13}\text{C}\)-\(\text{CO}_2\) enrichment arising from labeled CAF demethylation was determined by mass spectrometry and expressed as the % increase from baseline. The instantaneously labeled \(\text{CO}_2\) excretion rate was calculated as percent of administered labeled CAF at each sampling time. The cumulative labeled \(\text{CO}_2\) excretion rate was calculated from the area under the curve of the instantaneously labeled \(\text{CO}_2\) excretion rate as a function of time of 2, 4, and 6 hours after labeled CAF administration. CAF plasma concentration and CAF metabolite concentrations in urine samples were determined using HPLC.

CAF plasma clearance has been calculated as the ratio of the administered dose, assuming 100% bioavailability, to the area under the curve of CAF plasma concentration as a function of time between two consecutive doses. The demethylation process was estimated by the ratio of the number of methyl groups absent in the metabolites recovered in urine samples to the number of methyl groups contained in the molecules of the parent CAF.

The cumulative labeled \(\text{CO}_2\) excretion rate correlated with the CAF plasma clearance. CAF plasma clearance has been used as an indirect method of validating the CBT as a monitor of CYP 1A2, assuming that CAF plasma clearance correlates with CYP1A2-dependent CAF N-demethylation. This assumption should be valid because N-demethylation is the major route of CAF metabolism and CAF plasma clearance is expected to be sensitive only to hepatic intrinsic clearance. Because CAFD is a drug with a low extraction ratio and low protein binding, CAF plasma clearance is not expected to be influenced either by hepatic blood flow or by protein binding. The correlation between cumulative \(^{13}\text{C}\)-\(\text{CO}_2\) excretion rate and CAF plasma clearance already has been found in smoking and nonsmoking adults.

This method allowed us to describe the maturation profile of CAF N-demethylation as a function of age. No detectable change in expired \(^{13}\text{C}\)-\(\text{CO}_2\) from basal values was observed in neonates and young infants, whereas changes were measurable in all infants older than 33 days’ postnatal age and older than 45 weeks’ postconceptional age.

These changes parallel those of CAF plasma clearance and of demethylation ratio calculated from the urine data. CAF plasma clearance increases with postnatal age according to a single exponential curve. The plateau is reached during the second trimester of life and accounts for \(~60\%\) of all methyl groups. Demethylated metabolites are detectable as soon as 22 days’ postnatal age and 34 weeks’ postconceptional age.

Maturation of N-Demethylation of CAF During Puberty

The use of the CBT also has allowed study of the maturation of N-demethylation of CAF during puberty. Lambert and colleagues measured the changes in \(\text{CO}_2\) excretion rate after a 3 mg/kg administration of CAF labeled on the N3 methyl group in 62 subjects 3 to 20 years of age.

The labeled \(\text{CO}_2\) excretion rate was higher in children before puberty than in adults, and decreased with increasing age. Using the five pubertal stages of Tanner, Lambert and colleagues showed that the labeled \(\text{CO}_2\) excretion rate decreased with increasing pubertal maturation. The maturational profile during puberty differed by gender. The excretion rate of adult patients was reached earlier in puberty in girls (early puberty) than in boys (midpuberty). These changes in \(\text{CO}_2\) excretion rate suggest decreasing enzyme function during puberty and a different maturational profile according to gender.

Effect of Growth Hormone (GH) Therapy in GH-deficient Children on Demethylation of CAF

The use of the CBT allowed Levitsky and associates to study the effect of GH therapy in GH-deficient children on cytochrome P-450-dependent 3-N-demethylation of CAF. Six 4- to 15-year-old GH-deficient children received CAF labeled on the 3-N-methyl group as a single 3 mg/kg oral dose before and after a 4-week treatment with human GH, 0.1 IU/kg sc, three times a week. The 3-N-demethylation of CAF as measured by the CBT was significantly decreased after 1 month of GH therapy, suggesting a possible role of GH in the expression of CYP 1A2.

Enantioselectivity

There are no available data in the literature on the use of SIL in pediatric pharmacology for the study of enantioselectivity of drug metabolism. Using stable isotopes in adults, a highly stereoselective metabolism has been demonstrated for 4-hydroxylation of debrisoquine and the metabolism of other enantiomers. In children, changes related to enzymatic maturation may affect significantly the relative rate of biotransformation of enantiomers as a function of age.

PHARMACOKINETIC STUDIES

Using stable-isotope tracer methods, it is possible to perform pharmacokinetic studies that measure steady-state values and evaluate time-dependent and dose-dependent pharmacokinetic changes without exposing the subject to radiation, without creating radioactive waste, and without withholding necessary medication.

Time-dependent Pharmacokinetic Studies

Serial kinetic studies during maintenance therapy using SIL have been used in children to show time-dependent kinetic changes at steady state without need to interrupt the ongoing treatment and without exposure to radioactivity. A unit dose is replaced, totally or in part, by an equal amount of the labeled drug. Mass spectrometry allows one to study separately the kinetics of both the labeled and the unlabeled compound, using the same blood samples.

Autoinduction of Drug Metabolism

Carbamazepine (CBZ) is used in children for the treatment of partial seizures. The decrease in steady-state plasma concentrations of CBZ during long-term
Bertilsson and colleagues21 used tetraduterium-labeled CBZ in three 10- to 13-year-old children. A preliminary study in animals ruled out an isotope effect.22 Patients were given equimolecular amounts of labeled and unlabeled CBZ as an initial oral single dose. The plasma concentrations of the two forms of CBZ were determined simultaneously by mass spectrometry during the subsequent 4 days. The single oral dose kinetics of CBZ and CBZ-D4 were almost identical, indicating no isotope effect of deuterium labeling in these patients.

Maintenance therapy with unlabeled CBZ was started on day 5. On three separate occasions during the first 5 months of maintenance therapy, a portion of the CBZ dose was replaced by an equivalent amount of labeled CBZ. The plasma kinetics was studied after each of these doses. The steady-state CBZ total plasma concentrations during multiple dosing were lower after dose 3 (days 21–36) and dose 4 (~5 months) than after dose 2 (day 6). They were two times lower than the theoretic steady-state plasma concentrations predicted using the kinetic parameters obtained from the initial single-dose experiment. But they were close to those predicted using the kinetic parameters obtained after labeled CBZ administrations during multiple dosing. There was a considerable increase (~0.7 to 1.9 times) in plasma clearance between dose 1 and dose 3 without subsequent increase.

Because CBZ is eliminated primarily via metabolism, changes in kinetic parameters may be attributed to changes in metabolism. This study demonstrated the autoinduction of CBZ metabolism and described its time course (occurring rapidly; maximum, within 2–4 weeks).

Drug Interactions

Other time-dependent kinetic changes may be studied in children using SIL, including induction of biotransformation, inhibition of biotransformation,23 and the effect of age during long-term therapy.

Dose-dependent Pharmacokinetic Changes

The ability to study by SIL also holds true for dose-dependent kinetic changes, ie, nonlinear kinetics, performing stable isotope-labeled studies at different steady-state plasma concentrations.

Placental Transfer of Drugs

Brazier and colleagues developed a model using labeled theophylline in the pregnant ewe to investigate the placental transfer of drugs.24 This method allows one to conduct simultaneously, in the same animal, infusions with the labeled drug to the fetus and with the unlabeled drug to the mother, and to study the kinetics of both labeled and unlabeled drug in both fetus and mother.

This method is of more limited use in humans because injection of drug in the umbilical vein of the fetus is possible, but serial sampling of the umbilical blood is not. The staggered stable isotope administration technique therefore may be of great potential interest to evaluate placental transfer and to calculate drug entry half-life. By infusing intravenously to the mother a series of different stable isotope-labeled forms of the same drug at different times before a single collection of fetal blood via a puncture of the umbilical vein for diagnostic or therapeutic purposes, one can obtain the same information about the drug’s distribution as would be obtained by infusing a single dose of the drug and performing serial collections of umbilical venous blood.25 This technique, however, has several drawbacks. Synthesis of a series of stable isotopes of a drug is expensive. Presence of several stable isotopes of a drug may create analytic difficulties by increasing problems with overlap and interference by endogenous substances. One must have an approximate idea of the time required for the umbilical drug concentration to attain equilibrium to select proper times for administration of stable isotope-labeled analogues and specimen collection. However, it would also have to be known for serial sample collections using alternative techniques. The mother would be exposed to the potential morbidity of several intravenous infusions of the drug being investigated.

Other Studies

The staggered stable isotope administration technique requiring only a single biologic sample also could be applied to the measurement of the rate of entry of drugs into cerebrospinal fluid or tissues other than blood (liver or kidney) as part of a routine diagnostic procedure (lumbar puncture, renal or liver biopsy).

Other kinetic studies of potential interest in pediatric pharmacology include the study of the enantioselectivity of kinetics of drugs, and, particularly, the determination of absolute and relative bioavailability in early infancy.

Study of the Enantioselectivity of Kinetics of Drugs

Stable isotope-labeled isomers of a drug have been used to study stereospecific aspects of a drug’s disposition in adults,26–28 but, to our knowledge, not in children.

Studies of Drug Bioavailability and Bioequivalence

Bioavailability is defined as the rate and extent of absorption of a drug from its dosage form into the systemic circulation. Absolute bioavailability is measured as the ratio of the availability of a pharmaceutical formulation of a drug to the availability of the same drug after intravenous administration. Relative bioavailability is measured as the ratio of the availability of two nonintravenous pharmaceutical alternatives of the same drug. Bioequivalence is defined as the equivalent bioavailability of two or more pharmaceutical alternatives.

The primary advantage of the isotopic methods is that the drug can be administered concomitantly by either of two routes (eg, parental or oral) or in two formulations (eg, solutions or solid dosage). Thus, a single set of blood samples serves to describe the time course of the routes or formulations being compared. The concomitant administration reduces in-
trastubject variability inherent in dual administration of the conventional crossover designs, considering that each subject serves as its own real time control. To achieve equivalent statistical certainty, stable isotope can reduce the number of subjects by at least 50%, resulting in reduced cost. The single assay for both forms further reduces variation. The method minimizes both drug exposure and discomfort to the subject by reducing the time and number of samples collected, and there is no need for the individual to undergo the procedure more than once. Furthermore, this technique is well-suited to pulse administration, wherein the kinetics of a single dose during multiple or chronic dosing regimens can be compared with single-dose kinetics.

STUDY OF COMPLIANCE

SIL also could be used in children as tracer to determine compliance. The primary problem with the use of stable isotopes in compliance studies is the cost of the tracer, a biologically acceptable substance labeled with a rare stable isotope (13C, for example). To minimize the cost of such a study, Schwarcz et al proposed using the cheapest enriched light isotope that is available, namely, deuterium. For drugs administered as liquids (eg, insulin), D2O could be included in the drug as a diluent. Deuterated glucose could be used as a filler in solid drugs. Using this method, Schwarcz et al could detect failure to comply with prescribed dose at the 10% deviation level, in adult subjects. There is no available example of such a use in children.

EFFECT OF EXOGENOUS PANCREATIC ENZYMES

The use of 13C-labeled lipids to detect fat malabsorption in children is of particular advantage in a pediatric population because of the simplicity of tests based on 13C-CO2 measurements of respiratory CO2: the collection of fecal samples is inconvenient for outpatients, expensive hospitalization is required, and stool analysis is unpleasant to laboratory technicians.

Fat malabsorption results either from an absence of bile acids or pancreatic lipase or from inadequate intestinal mucosa. Watkins et al administering 10 mg/kg 1-(13C)-trioctanoin showed that children with normal fat absorption excreted a total of 25% ± 2.5% of the dose as 13C-CO2, by 2 hours, whereas those with steatorrhea, because of pancreatic insufficiency resulting from cystic fibrosis, excreted 3.5% ± 2.5% of the dose in the same period of time. The increase of 13C content in the breath reflects the activity of the enzyme lipase. When exogenous pancreatic enzymes were fed, the children with cystic fibrosis excreted less fat, and the 13C-CO2 excretion increased fourfold, showing that the treatment decreases fat malabsorption.

Of potential interest for the diagnosis of pancreatic amylase insufficiency is the cornstarch breath test commercially available. The active ingredient, cornstarch, a nonsynthetic pharmaceutic agent, is produced by a common plant and contains the stable isotope carbon 13. A reduced production of 13C-enriched CO2 traced in the exhaled air shows the presence of exocrine pancreatic insufficiency.

STUDY ON THE EFFECT OF DRUGS

Treatment of Helicobacter pylori Infection

Active chronic gastritis is clearly related to the presence of Helicobacter pylori, both in children and in adults. The prevalence of Helicobacter pylori infection in children diagnosed as having primary gastritis varies between 70% and 84%. Present methods for detecting Helicobacter pylori include techniques (bacterial cultures, urease tests, histologic examination of antral biopsy specimens) that require endoscopy and therefore are invasive and difficult to use in children.

The urea breath test is a noninvasive technique designed to identify the presence of urease activity in the gastrointestinal tract. The principle of the urea breath test is that in the presence of the enzyme urease, orally administered urea is hydrolyzed to CO2 and ammonia. If the urea carbon is labeled with either the stable isotope 13C or radioactive 14C, it can be detected in the breath as labeled CO2. Helicobacter pylori is the most common urease containing gastric pathogen, and therefore a positive urea breath test generally can be equated with the presence of a Helicobacter pylori infection. The 13C urea breath test results compare well with the 14C urea breath test results. The great advantage of the 13C-urea breath test in children is the absence of radioactive risk. Although the radioactive dose with 14C-urea is low, total avoidance is better. Furthermore, repetition of the test that will be required at intervals theoretically places the use of radioactive isotopes at a disadva-

tage. The urea breath test has proven to be very robust. The degree of sensitivity (96%), specificity (93%), and positive (83%) and negative predictive value (99%) of the 13C-urea breath test regarding cultures as gold standard in children corresponds to that reported in adults.

Eradication of Helicobacter pylori infections has proven difficult. There was a need for simple, non-invasive tests that will rapidly identify and separate therapeutic modalities according to their effectiveness. Graham et al showed that the 13C-urea breath test is fully the equal of any of the alternative invasive procedures in monitoring a clinical trial in which the treatment was tested for its ability to eradicate Helicobacter pylori infection.
estimated by the measurement of leucine flow in vivo.

This method was used to assess the effects of a short high-dose prednisone treatment (40 mg/m²/24 hours to a maximum of 60 mg/24 hours) in eight normal subjects on leucine metabolism from a primed continuous infusion of L-(1–13C)-leucine during both the postabsorptive and fed state.

Prednisone increased the flux of leucine coming from protein (protein catabolism), but did not modify protein synthesis. Protein balance (synthesis minus catabolism) became more negative in the post-absorptive state and failed to become positive in the fed state.

Although this study has not been performed in children, this type of study is of great potential interest in children on drug therapy.

Of potential interest are the metabolic studies on the influence of drugs on glucose turnover, nitrogen metabolism, and energy expenditure after administration of 13C-glucose, 15N amino acids and doubly labeled water, respectively.42

### EFFECT OF DRUGS ON MINERAL METABOLISM

Stable isotope techniques have been developed to assess Fe, Mg, and Zn metabolism.43 Shoemaker et al (1996)44 studied three children with hyperprostaglandin E syndrome and severe hypercalcemia. These children demonstrated Ca hyperabsorption that decreased after treatment with indomethacin.

In adults, numerous therapies for chronic bone-loss disorders include high-dose Ca supplementation, vitamin D (and its metabolites) therapy, calcitomin, and other antible resorptive drugs. As such approaches increasingly become used in children, isotopic studies offer a direct way to evaluate their effectiveness.

### TERATOGENICITY

In pharmacokinetic studies, the occurrence of isotope effect can lead to grossly misleading biologic and analytic results and therefore should be avoided. In mechanistic studies, isotope effects are used at their advantage. It is possible to elucidate which drug metabolic pathway leads to a teratogenic metabolite by labeling the drug with deuterium at various metabolic sites and determining in animals the metabolic site important for the formation of the teratogenic metabolite and that formation of the metabolite was inhibited by kinetic isotope effect.

### EFFECT OF DRUGS ON GASTRIC EMPTYING

Gastric emptying is frequently abnormal in gastro-esophageal reflux disease. Two commercially available tests, the 13C-sodium acetate and the 13C-octanoic acid breath tests look promising to study the influence of prokinetic drugs on gastric emptying of the liquid phase and the solid phase, respectively.46

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