INACTIVATION OF ISONIAZID BY CONDENSATION IN A SYRUP PREPARATION

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Inactivation of Isoniazid by Condensation in a Syrup Preparation*

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This paper reports the gross and rapid condensation of isoniazid in a commercial black-currant-flavoured syrup. In vitro *studies showed that the condensation was due, at least partly, to the glucose contained in the syrup, paper chromatography having demonstrated the presence of* D(+) *-glucose isonicotinoyl hydrazone. Controlled studies in human beings showed that the absorption of isoniazid from the preparation was considerably impaired by this condensation.*

It is concluded that sugars such as glucose, fructose, and sucrose—especially glucose—should not be used in isoniazid syrup preparations, and it is suggested that sorbitol, a stable non-carbonyl compound, might be a suitable substitute.

In paediatric practice, isoniazid is often administered in the form of syrup. A commercial isoniazid syrup with a palatable blackcurrant flavour was used in a controlled study of the value of chemoprophylaxis in close family contacts, aged less than 5 years, of infectious tuberculosis patients. On assay, the free isoniazid content of the syrup was found to be considerably less than that stated. Preliminary experiments indicated that the deficit of isoniazid was present in a bound form from which free isoniazid could be liberated by treatment with dilute mineral acids. The present paper describes these experiments and others undertaken to examine the implications of this finding.

MATERIALS AND METHODS

Syrup preparations

The isoniazid syrup investigated in this trial was a commercial preparation with a stated isoniazid content of 20 mg/ml and a pleasant blackcurrant flavour. The placebo was the same syrup without isoniazid. Both products were imported in 80-oz (2 273-cm^3) screw-capped, amber-coloured bottles. The syrup and placebo were stored at room temperature (approximately 26°C). All the estimations reported here were made at room temperature.

Estimation of free isoniazid in the syrup

Direct method. Isoniazid syrup was diluted (1 in 1 000) with distilled water and the resultant solution diluted (1 in 2) with 0.2 N sulfuric acid. After varying intervals (see page 627), a 3-ml aliquot of this acid solution was treated with 0.3 ml of vanillin reagent (2 % vanillin in 25 % ethanol), and the optical density was determined at 380 nm (G. A. Ellard, personal communication) against the reagent blank within 2 minutes, using 1-cm light-path cells in a Unicam SP 600 spectrophotometer. The isoniazid content was then read from a calibration graph obtained with standard solutions of isoniazid (1 to 10 µg/ml) in 0.1 N sulfuric acid.

Extraction method. The method of Eidus & Little (1962) was used, with some modifications. In brief, 3 ml of a solution of the isoniazid syrup in distilled water (1 in 2 000) were first mixed with 1 ml of 0.1 N sodium hydroxide and 3.2 g of powdered ammonium sulfate in a 250-ml stoppered conical flask; the contents were then shaken together with 30 ml of a solvent mixture containing chloroform and butan-1-ol (7: 3) for 30 minutes in a rotary shaker. Next, 20 ml of the solvent extract were shaken for 15 minutes with 4 ml of 0.1 N sulfuric acid, and the isoniazid content in a 3-ml aliquot of the acid extract was estimated within 30 minutes, as in the direct method. Apart from free isoniazid, 12-13 % of the

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theoretical isoniazid content of glucose isonicotinoyl hydrazone is estimated by this method.

Estimation of total isoniazid in the syrup

For the estimation of the total isoniazid content-that is, the free and bound forms together–1 ml of the syrup was subjected to acid hydrolysis by treatment with 5 ml of 4 N hydrochloric acid for 15 minutes; the acid was then neutralized by the addition of 5 ml of 4 N sodium hydroxide and the solution was made up to 250 ml in distilled water. A further dilution (1 in 8) was made of the resultant solution in distilled water, and the isoniazid content was estimated by the extraction method.

Estimation of isoniazid and its metabolites in urine

Free isoniazid. Free isoniazid was estimated by the extraction method from a sample of 3 ml of urine diluted in distilled water (usually 1 in 10).

Isonicotinoyl hydrazones. The hydrazones present in urine were converted to free isoniazid by acid hydrolysis-that is, by treating 1 ml of urine with 1 ml of 0.5 N hydrochloric acid for 2 hours. Next, 1 ml of 0.5 N sodium hydroxide was added, the solution made up to 10 ml with distilled water, and the total isoniazid content determined by the extraction method. From this, the free isoniazid content (estimated as described above) was subtracted to obtain the hydrazone content as isoniazid equivalent.

Acetylisoniazid. Acetylisoniazid was estimated by the method of Venkataraman et al. (1968) without oxidation with potassium permanganate, after an initial acid hydrolysis of the urine (as above) followed by neutralization with alkali to eliminate interference from the hydrazones.

Isonicotinic acid. Urine was diluted with distilled water (1 in 25) and 1 ml of the diluted urine was used for the estimation of isonicotinic acid by the method of Nielsch (1958), which is also used for estimating, as isonicotinic acid, 40–50% of the isonicotinoyl glycine present in urine (Nielsch & Giefer, 1959).

The amounts of acetylisoniazid and isonicotinic acid present in the urine were expressed as the milligram equivalent of isoniazid.

Estimation of isoniazid in serum

Isoniazid was extracted from serum using the method described on page 625, but using 2 ml of 0.1 N sulfuric acid. For estimating serum isoniazid concentrations of 0.2 µg/ml or more, 0.5 ml of the acid extract was treated with 0.05 ml of vanillin reagent in 2-cm light-path microcells and the optical density was determined at 380 nm.

For determining isoniazid concentrations of less than 0.2 µg/ml, the fluorometric method of Scott & Wright (1967) was used, with the following modifications of Kailasam, Prema & Gangadharam (Tuberculosis Chemotherapy Centre, unpublished data). Thus, 1.5 ml of the acid extract, obtained as described in the previous paragraph, was neutralized with 0.1 ml of 1.0 N sodium hydroxide and then treated for 15 minutes with 0.4 ml of salicylaldehyde reagent. (This reagent was prepared just before use by mixing 3 volumes of 0.1% salicylaldehyde in 1% ethanol with 1 volume of 11.2 % acetic acid.) Next, 1.3 ml of a solution containing 0.385 M sodium acetate, 0.154 % sodium disulfite (disodium pyrosulfite, $Na_2S_2O_5$), and 0.1 N sodium hydroxide were added, followed by 0.05 ml of 2-mercaptoethanol (the PH of the solution at this stage was 5.6). After having been treated at 50°C for 10 minutes, the solution was cooled to room temperature and 3.5 ml of isobutyl alcohol and 2 g of powdered ammonium sulfate were added. The contents of the flask were thoroughly shaken by hand for 1 minute and then chilled in ice water. Finally, the isobutyl alcohol layer was transferred to a dry test-tube. While the extract was kept ice cold, its intensity of fluorescence was measured within 10 minutes, using a Beckman DU spectrophotometer with a fluorescence attachment.[1] Solutions of isoniazid in concentrations of 0.01 to 0.16 µg/ml in serum were used for the calibration graph.

Identification of sugars and hydrazones in both syrups by paper chromatography

Dilute solutions of the isoniazid and placebo syrups in distilled water, and standard solutions in distilled water of isoniazid, glucose, fructose, and D(+)-glucose isonicotinoyl hydrazone, prepared by the method of Fox (1953), were spotted qualitatively on a Whatman No. 1 filter paper; the paper was folded in the form of a cylinder and kept upright in a solvent system containing propan-2-ol and water (Zamboni & Defranceschi, 1954). The chromatogram was developed for 16-18 hours. After drying, the paper was exposed to cyanogen bromide vapours in a closed chamber and was then sprayed with benzidine reagent (0.5 g dissolved in a mixture of 20 ml of glacial

[1] This attachment contains a Corning filter No. 5860 (ultraviolet), which transmits a band of wavelengths centring at 360 nm.

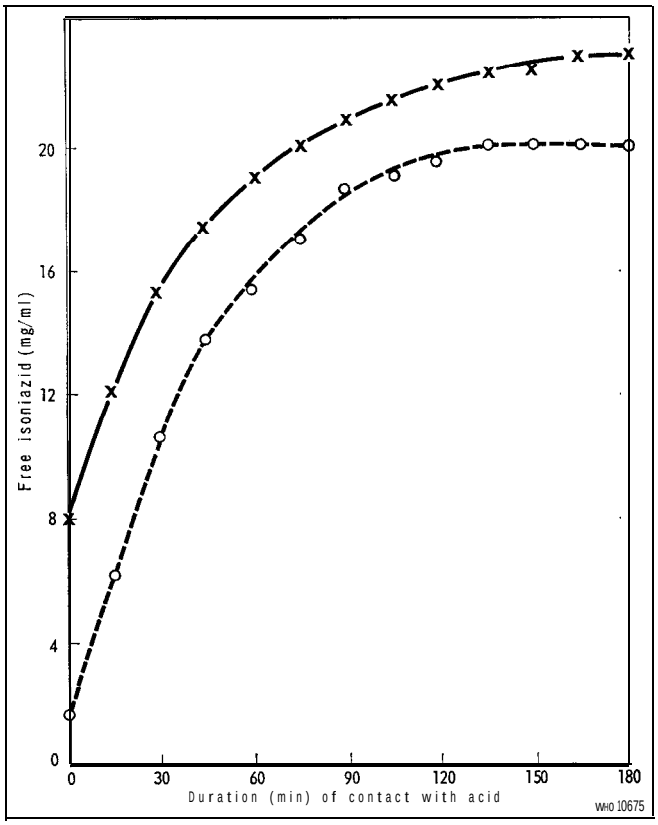

Fig. 1. Effect of acid hydrolysis of isoniazid syrup (solid line) and D(+)-glucose isonicotinoyl hydrazone (broken line)

acetic acid and 80 ml of absolute ethanol). Isoniazid and D(+)-glucose isonicotinoyl hydrazone produced yellow spots after exposure to cyanogen bromide, whereas glucose and fructose gave brown spots after spraying with benzidine reagent.

INVESTIGATIONS AND RESULTS

Presence of isoniazid in bound form in the syrup

The free isoniazid content of each of 3 samples of the isoniazid syrup was determined by the direct method immediately (within 1 minute of making the dilution with 0.2 N sulfuric acid), and thereafter at intervals of 15 minutes for 3 hours. The mean free isoniazid content of the 3 samples immediately after making the dilution in acid was 8 mg/ml, as compared with the stated content of 20 mg/ml. However, it increased steadily to the stated content the longer the isoniazid remained in contact with the acid (Fig. 1). These findings suggest that about 12 mg of isoniazid per ml–i.e., about 60% of the stated content-were present in the syrup in a bound form, being reconverted to free isoniazid after acid hydrolysis.

Fig. 1 also presents comparable data on the hydrolysis of D(+)-glucose isonicotinoyl hydrazone under identical conditions. The similarity in the reaction rates suggests that the bound form of isoniazid in the syrup was probably D(+)-glucose isonicotinoyl hydrazone.

The extraction method was employed to determine the free isoniazid content of a further 15 samples of the syrup from a different batch. The mean content was 5.9 mg/ml (range: 5.2–6.6 mg/ml) before acid hydrolysis and 20.6 mg/ml (range: 20.0–21.2 mg/ml) after acid hydrolysis, confirming the observation, made above, that a major proportion of the stated content of isoniazid was present in a bound form.

Sugar content of the placebo syrup

The placebo syrup contained, besides sucrose, 10 % liquid glucose (approximately 40 % dextrin, 20 % maltose, 20% glucose, and 20% water). Paper chromatography revealed the presence of fructose, presumably formed as a result of the break-down of sucrose.

Demonstration of isonicotinoyl hydrazone in the isoniazid syrup

A dilute solution of the isoniazid syrup in distilled water (1 in 250) yielded a positive result to the acetyl-isoniazid test of Eidus & Hamilton (1964), presumably owing to the presence of hydrazones. Whereas paper chromatography revealed the presence of D(+)-glucose and fructose (R_F- values 0.88 and 0.91, respectively) in the placebo syrup, the isoniazid syrup was found to contain isoniazid and D(+)-glucose isonicotinoyl hydrazone (R_F values 0.97 and 0.93, respectively) in addition to D(+)-glucose and fructose. These findings suggest that the reduction in the free isoniazid content was attributable, at least partly, to condensation of the isoniazid with the glucose present in the syrup.

Condensation of isoniazid in different solutions

To study the extent and speed of condensation of isoniazid in the blackcurrant-flavoured syrup and its constituent reducing sugars, the following experiment was undertaken. Isoniazid in a concentration of 20 mg/ml was dissolved in *(a)* water (control), *(b)* 70 % sucrose, *(c)* 5 % fructose, *(d)* 5 % glucose, *(e)* a mixture of 60 % sucrose, 5 % fructose, and 5 % glucose, and *(f)* the placebo syrup. All the solutions were stored in screw-capped bottles at 26°C, and their free isoniazid content was determined by the extraction method (without acid hydrolysis) on the second day (i.e., after 24 hours' storage) and on the tenth and thirtieth days. The findings are set out in Table 1 .

No loss of free isoniazid occurred in water (control). A slight loss occurred in the 70% sucrose and the 5 % fructose solutions, their free isoniazid content on the thirtieth day being 18.4 mg/ml and 17.2 mg/ml, respectively. Condensation was greater and more rapid in the 5 % glucose solution and in the sucrose-fructose-glucose mixture, the free isoniazid content being 14.2 mg/ml on the tenth day and 7.6 mg/ml on the thirtieth day for the former, and 11.4 mg/ml and 6.8 mg/ml, respectively, for the latter. Finally, condensation was greater and very rapid in the blackcurrant-flavoured syrup, whose free isoniazid content was 7.4 mg/ml on the second day-compared with 20 mg/ml in all the other solutions-and had decreased to 5.2 mg/ml by the thirtieth day. This may be explained partly by the fact that the blackcurrant-flavoured syrup, which contained 10 % liquid glucose, was more acidic (pH 4.3) than the other solutions and partly by the evidence from Table 2 that the speed of condensation of isoniazid with glucose was enhanced by decreasing the pH of the solution to 4.1.

Table 1. Condensation of isoniazid in different solutions

Solution	Free isoniazid content (mg/ml)		
	2nd day	10th day	30th day
water (control)	20.0	20.0	20.0
70 % sucrose	20.0	20.0	18.4
5 % fructose	20.0	19.2	17.2
5 % glucose	20.0	14.2	7.6
Mixture of 60 % sucrose, 5 % fructose, and 5 % glucose	20.0	11.4	6.8
Blackcurrant-flavoured syrup	7.4	6.6	5.2

Implications of the condensation of isoniazid in syrup

The finding that a substantial proportion (about 60–70%) of the isoniazid in the syrup was present in a bound form (page 627) does not necessarily imply that the tuberculostatic potency of the preparation was considerably impaired. Thus, it is possible that some or all of the bound isoniazid was converted into free isoniazid in the stomach by the action of the gastric juice, and then absorbed. To investigate this possibility, a study was undertaken in 6 healthy

Table 2. Influence of pH on the condensation of isoniazid in liquid glucose and glucose solutions

Solution	pH	Free isoniazid content (mg/ml)		
		2nd day	10th day	30th day
10 % liquid glucose	5.5	20.1	14.4	10.2
	4.1	11.3	11.3	10.3
5 % glucose	6.3	20.0	14.4	8.7
	4.1	10.9	11.2	8.9

children, all aged about 5 years. Three of them, selected at random, were given the isoniazid syrup in an intended dose of 15 mg of isoniazid per kg of body weight (based on the stated content of 20 mg/ml). As a control, the other 3 children received the same dose of isoniazid (15 mg/kg) in slightly sweetened dilute milk containing isoniazid in a concentration of 20 mg/ml (the isoniazid was added to the milk just before the dose was given). From each child, all the urine excreted during each of the 3 consecutive 2-hour periods immediately following medication was collected., All the 18 samples (i.e., 3 from each of the 6 children) were marked with code numbers and sent to the laboratory, where their content of isoniazid and its metabolites was estimated. The experiment was repeated a week later, isoniazid (in the same dose) being given in milk to the children who had received it in syrup on the first occasion, and *vice versa.*

It was found that 15.4 % of the dose administered in milk (control) was excreted in the urine as isoniazid or its metabolites during the first 2 hours, compared with only 4.6% of the dose given in the syrup. The corresponding proportions were 19.9% and 6.8%, respectively, during the second 2-hour period, and 13.5% and 4.5%, respectively, during the third 2-hour period. Thus, during the first 6 hours, 48.8 % of the dose administered in milk was excreted as isoniazid or its metabolites, compared with only 15.9 % of the dose administered in the syrup, the latter being 33% of the former. It is to be noted that the free isoniazid content of the syrup was 6.3 mg/ml–i.e., 32% of the stated content of 20 mg/ml. The pattern of urinary excretion–i.e., the composition of the total excretion as acetylisoniazid, hydrazones, isonicotinic acid, and isoniazid-was the same whether the isoniazid was administered in milk or in syrup. Thus, the findings of the first 6 hours fail to provide any evidence that the bound form was absorbed or converted to the free form in the stomach or the gut.

It was observed that, even when the isoniazid was given in milk, only 48.8% of the dose administered was excreted in the first 6 hours. It was decided, therefore, to study the amount excreted over a longer period (24 hours) and to determine the serum isoniazid concentrations attained after administration of the drug in syrup and in milk.

For organizational convenience, the study was undertaken in 4 healthy adults aged 26-32 years. Each received a uniform dose of 600 mg of isoniazid in 30 ml of milk on one occasion and, on another occasion, as 30 ml of the syrup investigated. The total urine excreted during the 24 hours after administration of the drug (i.e., during the consecutive periods 0–6, 6–10, and 10–24 hours) was collected, blood samples being taken 1½ and 10 hours after medication. The procedures used were the same as for the study in children, and the findings are set out in Table 3.

With regard to the total excretion of isoniazid and its metabolites, 50.9% of the dose administered in milk was excreted during the first 6 hours, compared with only 22.9% of that given in the syrup. Over the whole 24-hour period, 82.4% of the dose administered in milk was excreted, compared with 46.8% of that given in the syrup, the latter being 57 % of the former.

The mean serum isoniazid concentrations were 10.9 µg/ml 1½ hours following the administration of isoniazid in milk and 3.1 µg/ml after it was given in syrup; the corresponding values at 10 hours were 0.8 µg/ml and 0.5 µg/ml.

In summary, there is strong evidence that substantially less isoniazid was absorbed from the syrup than from the milk (control).

Absorption of isoniazid from the bound form in the syrup

The free isoniazid content of the syrup used for the study in adults was 6.5 mg/ml–i.e., 32.5 % of the stated content of 20 mg/ml (the remaining 67.5% being present in the bound form). Therefore it might be expected that the total excretion of isoniazid and its metabolites after the drug was given in syrup would be 32.5 % of that following its administration in milk, unless there were a contribution from the bound form in the syrup. During a 24-hour period, the observed proportion was appreciably higher–i.e., 57% (Table 3, last column), indicating that absorption from the bound form had occurred to some extent. Further calculations (not presented here) showed that about 9% of the bound form was excreted as isoniazid or its metabolites in the first 6 hours, 7 % in the next 4 hours, and 13 % in the next 14 hours–i.e., a total of 29% in the first 24 hours. A further investigation, in which 3 of the 4 adults studied earlier again received 30 ml of the isoniazid syrup, showed that less than 8% of the bound form was excreted during the second 24-hour period after medication. All 3 patients had serum isoniazid concentrations of <0.2 µg/ml 24 hours after taking the drug. The rate of excretion from the bound form was 1.5 % per hour during the first 6 hours; 1.8% per hour during the next 4 hours;

Table 3. Excretion of isoniazid and its metabolites in urine during the 24 hours following administration of the drug in milk (control) and in syrup

Compound	Excretion in urine as percentage of administered dose of isoniazid*								
	0-6 hours		6-10 hours		10-24 hours		O-24 hours		
	Milk	Syrup	Milk	Syrup	Milk	Syrup	Milk (a)	Syrup (b)	(b) as % of (a)
Acetylisoniazid	20.5	10.6	10.0	5.7	6.5	6.4	37.0	22.7	61
Hydrazones	3.6	1.8	1.5	0.9	0.9	1.0	6.0	3.7	62
Isonicotinic acid	8.1	4.8	4.5	2.8	3.2	3.9	15.8	11.5	73
Isoniazid	18.7	5.7	3.5	1.9	1.4	1.3	23.6	8.9	38
Total	50.9	22.9	19.5	11.3	12.0	12.6	82.4	46.8	57

* Mean of the results for 4 adults.

0.9% per hour during the 14 hours after that; and <0.3% per hour in the subsequent 24-hour period. The decreasing trend suggests that little excretion is likely to occur 48 or more hours after medication. It may be concluded, therefore, that about 37% of the isoniazid present in bound form in the syrup could have been converted into free isoniazid in the body.

DISCUSSION

Isoniazid is known to be incompatible with aldehydes and ketones (Todd, 1967) owing to condensation of these compounds with isoniazid. Sugars such as glucose and fructose, containing aldehyde or ketone groups, are also known to form condensation products with isoniazid. Nevertheless, there has been no report so far about the condensation of isoniazid in syrup preparations of the kind often used in paediatric practice. The commercial isoniazid syrup investigated was found to have a free isoniazid content of 6-8 mg/ml, as against the stated content of 20 mg/ml, the deficit being present in a bound form from which free isoniazid could be liberated by acid hydrolysis. *In vitro* studies showed that substantial condensation of isoniazid occurred within 24 hours, and paper chromatography demonstrated the presence of D(+)-glucose isonicotinoyl hydrazone, indicating that the condensation was due, at least in part, to the glucose in the syrup.

Peters & Hayes (1966) studied the metabolism of glucose isonicotinoyl hydrazone in dogs after intravenous injection, and discovered that less than 30% of the hydrazone was converted to isoniazid in the body. Kakemi et al. (1965) found poor absorption of the glucose derivative of isoniazid in their studies of urinary excretion in man. These findings suggest that a considerable proportion of the glucose isonicotinoyl hydrazone in the isoniazid syrup might not have been available as isoniazid. Controlled studies in human subjects at this Centre showed that absorption from the bound form was rather slight (37 %). Furthermore, the evidence that the relative excretion of hydrazones in the urine was not significantly elevated (Table 3) suggests that the bound form that had been absorbed was probably broken down to isoniazid in the stomach or gut. Thus, the amount of free isoniazid available must have been less than 60% of the stated content (32.5 % + 37 % x 67.5 %, suggesting that the potency of the isoniazid syrup studied at this Centre may have been impaired by the condensation of isoniazid.

These findings suggest that syrup preparations of isoniazid should be assayed periodically and that the methods employed should be specific for the determination of free isoniazid.

Manufacturers would be well advised to avoid the inclusion of sugars such as glucose, fructose, and sucrose in syrup preparations of isoniazid. Sorbitol, a stable non-carbonyl compound, may

Table 4. Effect of storage at 26°C on the free isoniazid content of a syrup preparation of isoniazid in sorbitol

Duration of storage (months)	No. of samples tested	Free isoniazid content (mg/ml)	
		Mean	Range
None [a]	6	32.2	31.2-33.6
3	8	31.2	29.7-34.6
4	7	31.5	30.0-34.6
5	7	32.3	30.0-33.6
6	7	32.2	30.0-33.2
9	7	31.1	30.0-32.3
12	7	29.8	28.8-30.6
15	7	29.7	28.8-30.6
18	7	29.8	29.4-30.6
36	7	26.5	25.2-28.6

[a] Tested immediately on receipt.

be a suitable substitute; however, when administered in high dosage, it is known to produce diarrhoea (Peters & Lock, 1958; Goodman & Gilman, 1965). At this Centre, the incidence of diarrhoea over a 3-month period was 20% (unpublished data) when a syrup preparation of isoniazid (10 mg/ml) in sorbitol was administered twice weekly to 230 children aged less than 5 years (average dose of sorbitol: 13.6 g), and in 8 cases the syrup had to be discontinued for this reason. However, at a later stage, when another isoniazid syrup (30 mg/ml) in sorbitol (average dose of sorbitol: 4.2 g) was administered to 130 children for 1 year, diarrhoea was not a problem. Furthermore, when the latter preparation was stored at 26ºC, it showed no loss of free isoniazid in the first 6 months, and only a slight loss (7%) during the subsequent 12 months (Table 4). It may be concluded, therefore, that sorbitol is a suitable vehicle for syrup preparations of isoniazid, provided that the quantity of syrup administered is small.

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RÉSUMÉ

INACTIVATION DE L'ISONIAZIDE, PAR CONDENSATION, DANS UN SIROP

On a dosé l'isoniazide libre dans un sirop commercial aromatisé au cassis utilisé au Centre de Chimiothérapie de la Tuberculose, à Madras (Inde). Alors que la teneur en isoniazide indiquée par le fabricant était de 20 mg/ml, la concentration réelle était de 6-8 mg/ml seulement; le reste de l'isoniazide, sous forme combinée, a pu être extrait par hydrolyse acide. Des études *in vitro* ont montré que la condensation de l'isoniazide s'opérait dans les 24 heures et était due en partie au glucose présent dans la préparation: la chromatographie a mis en évidence de l'isonicotinyl-hydrazone de glucose.

Six jeunes enfants ont reçu alternativement une dose de 15 mg/kg d'isoniazide sous forme de sirop commercial et une dose identique du composé dans du lait. Dans les 6 heures suivant la prise du médicament, l'excrétion urinaire de l'isoniazide ou de ses métabolites a atteint 15,9% dans le premier cas et 48,8% dans le second.

Quatre adultes ont reçu 600 mg d'isoniazide, la première fois sous forme de 30 ml de la préparation commerciale, la seconde fois dans du lait. Après 24 heures, 46,8% de la dose donnée en sirop avait été excrétée et 82,4% de la dose donnée dans du lait. Après 1 heure ½, la concentration sérique moyenne de l'isoniazide atteignait 3,1 μg/ml dans le premier cas et 10,9 μg/ml dans le second; après 10 heures, les valeurs correspondantes étaient de 0,5 et 0,8 μg/ml. Il est apparu qu'une faible proportion (environ 37%) de l'isoniazide combiné était absorbée.

Il semble démontré, par ces observations, que l'absorption de l'isoniazide présenté dans le sirop commercial est considérablement entravée par suite d'un phénomène de condensation. Il est conseillé de ne pas utiliser, dans de telles préparations, des sucres comme le glucose, le fructose ou le saccharose, et de s'adresser à un produit de remplacement comme le sorbitol, composé stable et dépourvu de groupement carbonyle. Un sirop au sorbitol renfermant 30 mg/ml d'isoniazide, conservé à 26°C, n'a rien perdu de son activité au cours des 6 premiers mois, et sa teneur en isoniazide libre ne s'est abaissée que de 7% après un nouveau délai de 12 mois.

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