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ISOSORBIDE AS AN ORAL OSMOTIC DIURETIC

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This invention relates to the use of 1,4-3,6-dianhydro-D-glucitol as a diuretic. More particularly, it involves the process of producing diuresis in mammals by the oral administration of 1,4-3,6-dianhydro-D-glucitol (commonly referred to as isosorbide).

It is known in the art that various hexitols such as sorbitol and mannitol can be used as osmotic diuretics. However, intravenous administration of these materials is generally considered necessary in order to achieve an effective blood level since the hexitols are slowly absorbed in the gastro-intestinal tract when administered orally. Thus, the hexitols as a group are not considered to be pharmacologically effective as oral osmotic diuretics.

An object of this invention is to provide a process for producing diuresis in mammals.

Another object of this invention is to provide a process for producing diuresis by the administration of an orally effective osmotic diuretic.

A further object of this invention is to provide a process for producing diuresis by the administration of an orally effective osmotic diuretic which is not extensively metabolized before it exerts the desired physiological action, which has indicated freedom from objectional physiological side effects and which is largely excreted unchanged in the urine.

The above and other objects will become apparent from the following description of the invention.

It has been discovered that isosorbide possesses all of the desirable properties that are required for an effective oral osmotic diuretic. Isosorbide can be prepared in various suitable oral dosage forms such as tablets and suitably flavored liquids. Isosorbide is very soluble in various suitable vehicles. A 50% solution of isosorbide in water can be readily prepared.

Because of the fact that isosorbide is effective as an osmotic diuretic when administered orally, a rapid rate of ingestion and a better dosage rate control is obtainable than through intravenous administration. Further, by the process of administering concentrated liquid dosage forms or tablets of isosorbide little or no fluid is ingested to add to the amount of fluid to be removed by diuresis as in the case of administering hexitols intravenously. The use of isosorbide as an oral diuretic has the additional advantage

of making it possible for the patient to administer the drug to himself at required intervals without the attendance of medical personnel. However, when desirable, isosorbide may also be administered intravenously to obtain osmotic diuretic effects.

Isosorbide may be used generally in pathological conditions where treatment with a diuretic is indicated. In addition, it may be used where an osmotic effect is desired.

In the many studies performed it has been determined that practically all of the isosorbide that has been administered orally is ultimately excreted in the urine. Based upon measurements with randomly labeled isosorbide-C^{14} it has been determined that following oral intubation of isosorbide-C^{14} to male and female rats more than 97% of the ingested dosage is excreted, rapidly and essentially unchanged in the urine. This indicates a particularly advantageous property, namely, that nearly all of the administered diuretic is available at one time in the kidney to exert its osmotic effect upon the process of water excretion without a diversion of the active material away from the site of desired action to other sites for other modes of excretion.

The recommended oral dosage level of isosorbide may vary depending on the amount of diuresis desired. It has been determined that the dose to produce the desired amount of diuresis will usually fall in the range of from about 0.3 gm./kg. to about 3.0 gm./kg. of body weight. However, this range may be broadened by reducing or increasing the dosage depending on the nature of the case.

The following data is set forth in order to more clearly illustrate the nature of this invention; however, the invention is not intended to be limited by these examples.

EXAMPLES 1–10

One hundred fourteen rats in this study were selected from a colony continued from the Sprague-Dawley Strain Caesarean Derived Colony of Charles River Breeding Laboratories. Both male and female test animals weighed 145±15 grams. The animals used were approximately six weeks old. Five males and five females were intubated orally with a 50% solution of isosorbide in water at each of nine dosage levels. A control group consisted of twelve male and twelve female rats. Urinary volumes were measured for three periods during the twenty-four hour period prior to intubation with isosorbide and again for three periods during the twenty-four hour period after orally administering isosorbide. The following chart sets forth the various dosage levels given the animals and the quantity of urine excreted during the various time periods before and after administration of the drug. Food and water was permitted ad libitum during all test periods.

Example	Dosage (gm./kg.)	Sex	Urinary Output (ml.) Prior to Oral Admin. of Isosorbide			Urinary Output (ml.) After Oral Admin. of Isosorbide		
			(−24) to (−20) hr.	(−20) to (−16) hr.	(−16) to (0) hr.	(0) to (+4) hr.	(+4) to (+8) hr.	(+8) to (+24) hr.
1	0.0	M[1]	1.5	1.0	2.1	1.5	0.6	4.0
		F[2]	1.6	0.8	3.2	1.5	1.0	4.0
		Av. M+F	1.6	0.9	2.6	1.5	0.8	4.0
2	1.58	M	1.1	0.8	2.1	2.5	0.9	3.8
		F	1.1	0.9	2.3	2.8	1.0	4.8
		Av. M+F	1.1	0.8	2.3	2.7	1.0	4.2
3	2.00	M	0.9	0.8	3.9	3.8	1.2	6.6
		F	1.4	0.9	1.6	3.5	1.0	5.3
		Av. M+F	1.2	0.8	2.8	3.7	1.1	5.9
4	2.5	M	1.0	0.7	4.1	4.0	1.3	6.1
		F	0.9	0.2	3.7	3.1	1.3	5.7
		Av. M+F	1.0	0.4	3.9	3.5	1.3	5.9
5	3.15	M	2.0	0.7	4.3	4.9	1.7	5.7
		F	1.3	0.5	1.7	4.0	1.1	3.9
		Av. M+F	1.6	0.6	3.1	4.5	1.4	4.7

Example	Dosage (gm./kg.)	Sex	Urinary Output (ml.) Prior to Oral Admin. of Isosorbide			Urinary Output (ml.) After Oral Admin. of Isosorbide		
			(−24) to (−20) hr.	(−20) to (−16) hr.	(−16) to (0) hr.	(0) to (+4) hr.	(+4) to (+8) hr.	(+8) to (+24) hr.
6	4.0	M	1.2	0.8	3.1	4.5	1.8	4.8
		F	0.6	0.4	4.5	5.3	1.5	5.4
		Av. M+F	0.9	0.6	3.8	4.9	1.6	5.1
7	5.0	M	0.8	0.8	4.1	5.6	2.9	5.0
		F	0.7	1.0	4.2	6.5	2.3	8.4
		Av. M+F	0.8	0.9	4.1	6.1	2.6	6.7
8	6.3	M	1.3	0.4	4.0	5.7	3.9	5.4
		F	0.8	0.5	4.1	6.7	3.1	5.8
		Av. M+F	1.0	0.4	4.2	6.2	3.5	5.6
9	7.9	M	0.6	0.6	2.4	8.9	3.8	4.7
		F	1.4	0.6	3.0	8.0	3.4	4.3
		Av. M+F	1.0	0.6	2.7	8.5	3.6	4.4
10	10.0	M	1.5	0.7	1.9	11.0	3.4	4.3
		F	1.0	0.4	4.6	10.5	3.9	4.8
		Av. M+F	1.2	0.6	3.3	10.7	3.7	4.6

[1] Male. [2] Female.

The efficacy indicated above was confirmed in additional detailed studies in dogs. These tests included one year oral chronic toxicity studies wherein the dogs were fed up to 12 gm./kg. per day of isosorbide and no indication of toxicity was observed.

To further illustrate the diuretic effect, six human subjects were administered isosorbide and their reactions were studied as noted in the following example.

EXAMPLE 11

Six normal human males, age 25–32, without any history of renal disease or viral illness were studied.

All pre-drug base line physical examinations and clinical studies were within normal limits.

Electrocardiogram, chest X-ray, complete blood count, serum electrolytes, creatinine, bromsulfalein retention, serum glutamic oxalacetic transaminase, cephalin flocculation, serum protein electrophoresis, serum osmolality and urinanalyses were all normal in each subject.

The oral doses of isosorbide, 1 gm./kg. body weight, were given on the third and seventh days of the test period to each subject. The dosage form administered consisted of a 50% aqueous solution of isosorbide containing 1% essence of ginger for flavor and 1% calcium cyclamate for sweetening. On the third day the subjects were well hydrated with an intravenous water load of 20 ml./kg. body weight of 2.5% dextrose in water. On the seventh day the subjects had been fasted overnight and given Pitressin to produce a hydropenic state. Thus, each subject was tested with the same oral doses of isosorbide in both hydrated and hydropenic states.

While the subjects were in a hydrated state on the third day of the test cycle the increase in urine flow as a result of the administration of 1 gm./kg. of isosorbide was between 10 and 15%. On the seventh day when the subjects were in a hydropenic state the increase in urine flow was between 40 and 50%. The increase in urine output resulted within 30 to 60 minutes after ingestion. Diuresis usually continued for at least 3 to 5 hours with peak effect noted usually between 60 and 90 minutes.

An increase in osmolar clearance was noted in all subjects, amounting to about 150% in hydropenic subjects and between 50 and 60% in hydrated subjects. The excretion rate of sodium was increased in all subjects in the order of 200 to 300% and correlated with urine flow and osmolar clearance.

Serum osmolality was increased 30 to 60 minutes after oral ingestion of isosorbide in both hydrated and hydropenic subjects. Plasma hemoglobin, red blood cell fragility, platelet count, reticulocyte count and hematocrit were not significantly altered during and up to 24 hours after administration of the drug.

Two-week follow up examinations of all subjects with hematologic and liver function testings showed no abnormality. The six subjects showed no ill effects and no measurable aberration of renal function after administration of oral isosorbide.

What I claim is:

1. The process of producing diuresis in mammals by the oral administration of isosorbide.

2. The process of producing diuresis in mammals by the oral administration of from about 0.3 gm. to 3.0 gm. of isosorbide per kilogram of body weight.

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