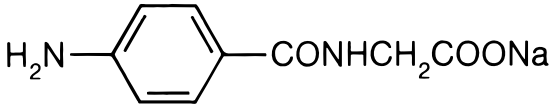
INJECTION

AMINOHIPPURATE SODIUM* "PAH"

DESCRIPTION

Aminohippurate sodium is an agent to measure effective renal plasma flow (ERPF). It is the sodium salt of para-aminohippuric acid, commonly abbreviated “PAH”. It is water soluble, lipid-insoluble, and has a pKa of 3.83. The empirical formula of the anhydrous salt is $C_9H_9N_2NaO_3$ and its structural formula is:



It is provided as a sterile, non-preserved 20 percent aqueous solution for injection, with a pH of 6.7 to 7.6. Each 10 mL contains: Aminohippurate sodium 2 g. Inactive ingredients: Sodium hydroxide to adjust pH, water for injection, q.s.

CLINICAL PHARMACOLOGY

PAH is filtered by the glomeruli and is actively secreted by the proximal tubules. At low plasma concentrations (1.0 to 2.0 mg/100 mL), an average of 90 percent of PAH is cleared by the kidneys from the renal blood stream in a single circulation. It is ideally suited for measurement of ERPF since it has a high clearance, is essentially nontoxic at the plasma concentrations reached with recommended doses, and its analytical determination is relatively simple and accurate.

PAH is also used to measure the functional capacity of the renal tubular secretory mechanism or transport maximum (Tm_{PAH}). This is accomplished by elevating the plasma concentration to levels (40-60 mg/100 mL) sufficient to saturate the maximal capacity of the tubular cells to secrete PAH.

Inulin clearance is generally measured during Tm_{PAH} determinations since glomerular filtration rate (GFR) must be known before calculations of secretory Tm measurements can be done (see DOSAGE AND ADMINISTRATION, *Calculations*).

INDICATIONS AND USAGE

Estimation of effective renal plasma flow.

Measurement of the functional capacity of the renal tubular secretory mechanism.

CONTRAINDICATIONS

Hypersensitivity to this product or to its components.

PRECAUTIONS

General

Intravenous solutions must be given with caution to patients with low cardiac reserve, since a rapid increase in plasma volume can precipitate congestive heart failure.

For measurement of ERPF, small doses of PAH are used. However, in research procedures to measure Tm_{PAH}, high plasma levels are required to saturate the capacity of the tubular cells. During these procedures, the intravenous administration of PAH solutions should be carried out slowly and with caution. The patient should be continuously observed for any adverse reactions.

Use caution when injecting this product into latex-sensitive individuals, since the vial stopper contains dry natural latex rubber that may cause allergic reactions.

* Formerly referred to as Sodium para-Aminohippurate.

Drug Interactions

Renal clearance measurements of PAH cannot be made with any significant accuracy in patients receiving sulfonamides, procaine, or thiazolesulfone. These compounds interfere with chemical color development essential to the analytical procedures.

Probenecid depresses tubular secretion of certain weak acids such as PAH. Therefore, patients receiving probenecid will have erroneously low ERPF and Tm_{PAH} values.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals have not been done to evaluate any effects upon fertility or carcinogenic potential of PAH.

Pregnancy

Pregnancy Category C. Animal reproduction studies have not been done with PAH. It is also not known whether PAH can cause fetal harm when given to a pregnant woman or can affect reproduction capacity. PAH should be given to a pregnant woman only if clearly needed.

Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when PAH is administered to a nursing woman.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

Clinical studies of PAH did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients.

ADVERSE REACTIONS

Hypersensitivity reactions including anaphylaxis, angioedema, urticaria, vasomotor disturbances, flushing, tingling, nausea, vomiting, and cramps may occur.

Patients may have a sensation of warmth or the desire to defecate or urinate during or shortly following initiation of infusion.

OVERDOSAGE

The intravenous LD_{50} in female mice is 7.22 g/kg.

DOSAGE AND ADMINISTRATION

For intravenous use only

Clearance measurements using single injection techniques are generally inaccurate, particularly in the measurement of ERPF. For this reason, intravenous infusions at fixed rates are used to sustain the plasma PAH concentration at the desired level.

To measure ERPF, the concentration of PAH in the plasma should be maintained at 2 mg per 100 mL, which can be achieved with a priming dose of 6 to 10 mg/kg and an infusion dose of 10 to 24 mg/min.

As a research procedure for the measurement of Tm_{PAH}, the plasma level of PAH must be sufficient to saturate the capacity of the tubular secretory cells. Concentrations from 40 to 60 mg per 100 mL are usually necessary.

Technical details of these tests may be found in Smith[1]; Wesson[2]; Bauer[3]; Pitts[4]; and Schnurr[5].

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to use, whenever solution and container permit. NOTE: The normal color range for this product is a colorless to yellow/brown solution. The efficacy is not affected by color changes within this range.

Calculations

Effective Renal Plasma Flow (ERPF)

The clearance of PAH, which is extracted almost completely from the plasma during its passage through the renal circulation, constitutes a measure of ERPF. Hence:

$$ERPF = \frac{U_{PAH}V}{P_{PAH}}$$

Where U_{PAH} = concentration of PAH (mg/mL) in the urine

V = rate of urine excretion (mL/min), and

P_{PAH} = plasma concentration of PAH (mg/mL).

Example: U_{PAH} = 8.0 mg/mL
V = 1.5 mL/min
P_{PAH} = 0.02 mg/mL

$$ERPF = \frac{8.0 \times 1.5}{0.02} = 600 \text{ mL/min}$$

Based on PAH clearance studies, the normal values for ERPF are:
men 675 ± 150 mL/min
women 595 ± 125 mL/min

Maximum Tubular Secretory (Tm_{PAH}) Mechanism

The quantity of PAH secreted by the tubules (Tm_{PAH}) is given by the difference between the total rate of excretion ($U_{PAH}V$) and the quantity filtered by the glomeruli (GFR x P_{PAH}). Hence:

$$Tm_{PAH} = U_{PAH}V - (GFR \times P_{PAH} \times 0.83)$$

The factor, 0.83, corrects for that portion of PAH which is bound to plasma protein and hence is unfilterable.

Example:
U_{PAH} = 9.55 mg/mL
V = 16.68 mL/min
GFR = 120 mL/min
P_{PAH} = 0.60 mg/mL
Then $Tm_{PAH} = 9.55 \times 16.68 - (120 \times 0.60 \times 0.83) = 100$ mg/min.
Average normal values of Tm_{PAH} are 80-90 mg/min.

The value of the expression $U_{PAH}V$, used in calculations of ERPF and Tm_{PAH}, may be found by determining the amount of PAH in a measured volume of urine excreted within a specific period of time.

These calculations are based on a body surface area of 1.73 m^2. Corrections for variations in surface area are made by multiplying the values obtained for ERPF and Tm_{PAH} by 1.73/A, where A is the subject surface area.

HOW SUPPLIED

No. 95 — Aminohippurate Sodium, 20 percent sterile solution for intravenous injection, is supplied as follows:

NDC 0006-3395-11 in 10 mL vials.

Storage

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].

REFERENCES

1. Smith, H.W.: Lectures on the kidney, University Extension Division, University of Kansas, Lawrence, Kansas, 1943.
2. Wesson, L.G., Jr.: "Physiology of the Human Kidney," New York, Grune & Stratton, 1969, pp. 632-655.
3. Bauer, J.D.; Ackermann, P.G.; Toro, G.: "Brays Clinical Laboratory Methods," ed. 7, St. Louis, Mosby, 1968.
4. Pitts, R.F.: "Physiology of the Kidney and Body Fluids," ed. 2, Chicago, Year Book Medical Publishers, 1968.
5. Schnurr, E.; Lahme, W.; Kuppers, H.: Measurement of renal clearance of inulin and PAH in the steady state without urine collection; Clinical Nephrology, *13*(1): (26-29), 1980.

Merck Sharp & Dohme Corp., a subsidiary of
MERCK & CO., INC., Whitehouse Station, NJ 08889, USA

Issued January 2011

Printed in USA