82 Correspondence

Figure. The centre of this field shows a finely stippled haemoglobinised megaloblast. Buffy-coat smear from Case 2. × 900. Stained Leishman.

In our infants treatment with folic acid but no other addition to diet was followed within a few days by complete normoblastic change associated with a reticulocyte response. As our facts do not fit with Professor Ozsoyu’s theories, we suggest the theories be changed to fit the facts.

References


M K Strelling
Department of Paediatrics,
Plymouth General Hospital,
Plymouth PL4 8QQ,
Devon

H B Goodall
Department of Pathology,
Ninewells Hospital,
Dundee, Angus

Sodium nitroprusside and RDS—primum non nocere

Sir,

There have been two reports on the use of sodium nitroprusside (NaNP) to reduce pulmonary vascular resistance in severe respiratory distress syndrome (RDS). This new indication for an old drug represents an innovative pharmacological approach to the treatment of pulmonary hypertension in the newborn. However, several aspects of this drug must be evaluated before the apparent success reported leads to widespread use in nurseries. As most neonatal therapeutic tragedies have occurred due to altered drug metabolism and disposition in the newborn infant, this aspect needs to be investigated urgently.
The metabolism of the drug has been studied in animals and adults.\textsuperscript{3} It is a salt of ferric cyanide with nitric acid, containing five cyanide (CN) molecules which are released nonenzymatically when the drug reacts with haemoglobin and blood, and tissue sulphhydryl groups. One free CN reacts with methemoglobin forming cyanomethemoglobin and the remaining four free CN are metabolised through other pathways. Most of the free CN is converted to thiocyanate, in the presence of thiols, via the hepatic and renal rhodanase systems. Thiocyanate is then excreted unchanged by the kidney, with a half-life of about one week in man. The free CN not rapidly converted to thiocyanate or carried in blood by erythrocytes binds to tissue cytochrome oxidases producing cytotoxic hypoxia resulting in cellular anaerobic metabolism. This is manifested by severe lactic acidosis, base deficits, increasing mixed venous oxygen, and subsequent death. As free CN binds rapidly to tissues and as erythrocyte CN has no toxic importance, measurement of blood CN concentration will not accurately reflect the degree of toxicity. Thiocyanate is also potentially toxic and fatalities are reported at significant plasma concentrations (20 mg/100 ml). Since detoxification of CN to thiocyanate is slow, significant concentrations of this metabolite will only appear after chronic administration of the drug.

Even though early detection of toxicity of this potent drug is necessary, serial measurements of CN and thiocyanate may not be helpful. Several investigators have recommended monitoring of metabolic changes (lactic acidosis, base deficits, and increased mixed venous oxygen) caused by anaerobic metabolism as the most sensitive and accurate indicators of early toxicity.\textsuperscript{3-4} However, this may be particularly difficult to assess in a neonate who is already hypoxic and acidic from ongoing RDS.

No data have been published about rhodanase activity and endogenous thiols availability in the premature newborn. Moreover, since good nutritional status is required for endogenous thiols availability, the poor nutritional status of these infants will further compromise the detoxification process. Other compounds —such as nitrate, thiocyanate, and hydroxocobalamin— have been reported to be protective against CN toxicity by supplying alternate metabolic pathways for CN.\textsuperscript{5-6} It is possible that pretreatment with these compounds exerts similar protection against CN toxicity in the neonate. Further investigation is needed, particularly on an evaluation of the pharmacology of these agents in the neonate.

Even though NaNP is a potent hypotensive drug, there are no specific dose recommendations based on dose-response or kinetic data. In children,\textsuperscript{7-8} it has been used with a broad range (0.5–12.0 \(\mu\)g/kg per min), the objective being to reduce the existing blood pressure to the desired level or to provide a ‘dry field’ for surgery. Toxicity also depends both on the rate of infusion and on the total amount of infused drug. In the newborn, Beverley \textit{et al.}\textsuperscript{8} used 120 \(\mu\)g/kg per hour rate or 2-88 mg/kg per day which equals the \(LD_{50}\) in rabbits and is close to an approximate \(LD_{50}\) in humans (3.6–12 mg/kg).\textsuperscript{9}

With so many uncertainties, the use of this drug in an attempt to reduce pulmonary vascular resistance in the newborn is not yet warranted. It is a toxic drug that has not been adequately studied in the newborn. Further studies to define metabolism, disposition, and toxicity in the newborn animal are needed before investigative studies on human neonates are performed. Later, prospective controlled studies on efficacy, pharmacodynamics, kinetics, and toxicity are necessary before this drug is used routinely in the human neonate. If a critically ill neonate treated for several days with NaNP for RDS were to succumb, the role of CN poisoning as a contributing factor to mortality might be a possibility.

More knowledge about this drug in the neonate must be obtained before it is used in infants with RDS. The rational and safe use of a drug such as NaNP can only be derived from adequate pharmacological studies in adult and newborn animals and human subjects.

References


Correspondence

TOMRIS TURME, JONATHAN M DAVIS, AND JACOB V ARANDA
Departments of Pediatrics, Pharmacology and Therapeutics, McGill University Faculty of Medicine, Montreal Children’s Hospital, Montreal, Quebec H3H 1P3, Canada

Editors’ note: See previous correspondence in the \textit{Archives} 1979, 54, 808-9.
Sodium nitroprusside and RDS--primum non nocere.

T Turmen, J M Davis and J V Aranda

*Arch Dis Child* 1980 55: 82-83
doi: 10.1136/adc.55.1.82

Updated information and services can be found at:
[http://adc.bmj.com/content/55/1/82.citation](http://adc.bmj.com/content/55/1/82.citation)

**Email alerting service**

These include:

Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

**Notes**

To request permissions go to:
[http://group.bmj.com/group/rights-licensing/permissions](http://group.bmj.com/group/rights-licensing/permissions)

To order reprints go to:
[http://journals.bmj.com/cgi/reprintform](http://journals.bmj.com/cgi/reprintform)

To subscribe to BMJ go to:
[http://group.bmj.com/subscribe/](http://group.bmj.com/subscribe/)