flow. We do not disagree that in mature animals (and possibly humans) the major cerebral arteries may show vasoactivity in response to changing patterns of flow, but we can find no data from the work of Drayton and Skidmore to support this assertion in the premature infant. The onus is on them to show that their method for measuring CBF correlates with any other independent method either in humans or in animals before we can accept that major cerebral arteries mediate cerebral autoregulation in the preterm neonate.

References


M I LEVENE, D H EVANS, L N J ARCHER, and D SHORTLAND
Departments of Child Health and Medical Physics, Leicester University School of Medicine, Leicester LE1 5WW

Drs Drayton and Skidmore comment:

Our finding of a large increase in cerebral artery blood velocity during the first 48 hours of life but no change in a measure of cerebral blood flow (CBF) has important implications for simpler Doppler techniques of assessing the cerebral circulation. Levene et al question whether limitations of our volumetric technique could explain the absence of any apparent increase in CBF.

It is true that if there had been progressive and unidentified constriction of the aortic isthmus over the 48 hours, CBF might indeed have risen. We know of only two detailed studies of sequential changes in the size of the isthmus both of which conclude that there is a progressive but slow relative increase in the diameter of the isthmus from birth. The isthmus has a different embryological origin from the ductus arteriosus, and is histologically indistinguishable from the rest of the aortic arch, which decreases the likelihood that it constricts in a similar manner to the ductus itself. Mode measurement of the diameter of the isthmus in our infants was frequently impossible but measurements from the real time image did not suggest that there were any progressive changes in diameter over the time course of our studies. The ovoid section of the aortic isthmus may introduce a small but constant error in our calculations but this is irrelevant to this discussion of change in velocity and flow.

In our opinion the basis for their calculation of potential error in our technique is inappropriate. Our own calculations, available from us on request, give a potential error in mean CBF of 9% for the preterm group and 16% for the term group, both well below the percentage change observed in cerebral artery velocity.

We may approach the same problem empirically by using the dispersion in our data that incorporates error and variation from all sources to calculate the confidence limits for any change. We can thus be 95% certain that any change in CBF between 1-5 and 48 hours was between +32% and −30% for the preterm group and +28% and −33% for the term group.

Levene et al conclude from the work of Kennedy et al that there is an increase in CBF in the first few days of life in dogs born at term. Their results, however, showed no increase in CBF over the first six days of life. Furthermore, Cooke et al, using venous occlusion plethysmography in the term infant, showed quite clearly that CBF was constant between three and 24 hours and that in fact flow was rather higher during the first two hours.4

Contrary to the statement of Levene et al, nowhere in our paper have we suggested that the major cerebral arteries perform the main role in regulating blood flow. Clearly in the normal brain perfusion is closely coupled to metabolic demand in the tissues and important local mechanisms regulating flow must exist. We do contend that the regulation of CBF is unusual in occurring at more than one arterial level including the major cerebral arteries. The quoted work of Ahmann et al suggests that in the anterior cerebral arteries of only three preterm infants studied the vessels had an immature muscle coat, whereas in eight infants of a wide range of gestations studied by ourselves the muscle wall was well developed. It seems illogical that Levene et al are prepared to accept that the major cerebral arteries of mature animals and humans are vasoactive, but are unwilling to accept the same for neonates. Our technique has been carefully validated in vitro. Appropriate animal models for validation in vivo are not currently available to us and we do not believe that acceptable gold standards for the measurement of CBF in the newborn human exist. We believe that investigators who rely on the use of mean cerebral artery blood velocity as a measure of CBF may be misled.

References


Interaction between chloramphenicol and acetaminophen

Sir,

Dr Choonara1 raises the possibility that the changes in chloramphenicol pharmacokinetics observed in our study2 were unrelated to acetaminophen. The pharmacokinetics of chloramphenicol could be influenced by many factors including age, underlying
Correspondence

disease, degree of hydration, fever, and other drugs. Study
designs and data analyses controlling for all these variables
are difficult and sometimes impossible in very sick
patients. The studies of Nahata et al and Toumanen et al
included many patients with these confounding variables.
Nahata et al studied 10 children with infection of the
central nervous system, four of whom received phenobar-
bital or phenytoin, or both; these are both known to induce
hepatic enzymes. One child also received acetaminophen.
Toumanen et al studied 44 children with bacterial meningi-

gits, 11 of whom had seizures requiring anticonvulsants.
All 44 children were feverish (38.5 to 41°C). In contrast,
four of our five patients had epiglottitis, an illness of rapid
onset and short duration. They had previously been in
good health and had not received any medication before
presenting with breathning difficulty. When studied 48–72
hours after chloramphenicol had been started, all five were
well hydrated and only one was feverish (38.1°C). Nahata
et al reported an increase in chloramphenicol and chlor-
amphenicol succinate kinetics in their 10 children. The
mean area under the curve (mg/l/hour) and plasma half
life t 1/2 (hours) for their patients when first studied were
similar to those in our patients (105-7 and 3-0 compared
with 112-2 and 3-0). These authors repeated their kinetic
studies two to 17 days after the first and found that the
mean area under the curve and t 1/2 had decreased to 79.5
and 2.3, respectively, compared with 28.7 and 1.2 in our
patients (48–72 hours after the first study). They found that
patients who had the greatest area under the curve at the
time of the first study had the greatest decline. We found
no such correlation. The mean (SD) change in the area
under the curve among our patients was 74±1 (6-9)%., the
patient with the smallest initial area under the curve had a
77-7% change and the patient with the largest had a 73-5%
change.

It is possible that the changes we observed in chloram-
phenicol pharmacokinetics were independent of acetami-
nophen. We agree with Dr Choonara that information on
the pharmacokinetics of chloramphenicol after acetami-
nophen therapy or the use of control patients who
concurrently received acetaminophen and chlorampheni-
col followed by chloramphenicol alone would have been
ideal. Hepatic microsomal enzyme activation may take
days to weeks to return to the preactivated level after
withdrawal of the inducing agent. The decrease in the
urinary excretion of free chloramphenicol with an inverse
relative increase in the glucuronide conjugate, and the
magnitude of change in the kinetic profile of the drug in
our patients who were studied on two occasions with 72
hours allowed us to conclude that a chloramphenicol-
acetaminophen interaction existed as we had no other clear
explanation for these changes. Our conclusion also
remains that therapeutic drug monitoring is necessary
whenever drugs with a narrow therapeutic index such as
chloramphenicol are used.

References
1. Choonara IA. Interaction between chloramphenicol and aceta-
2. Spika JS, Davies DJ, Martin SR, Belamy K, Rex J, Aranda JV.
Interaction between chloramphenicol and acetylsalicylic acid.
3. Nahata MC, Powell DA. Chloramphenicol serum concentration
falls during chloramphenicol succinate dosing. Clin Pharmacol
4. Toumanen E, Powell KR, Marks MI, Laferriere CI, Almt-
iller DH, Sack CM, Smith AL. Oral chloramphenicol in the
5. Benet LZ, Schiner LB. "Pharmacokinetics: The dynamics of
drug absorption, distribution and elimination". In: Goodman
and Gilman’s The pharmacological basis of therapeutics. Gilman
AG, Goodman LS, Rall TW, Murad F (eds), 7th ed., New

J S Spika and J V Aranda
McGill University,
Montreal Children’s Hospital,
Montreal,
Quebec, Canada H3H 1P3

Neonatal typhoid fever

Sir,

In a recent article, Chin et al concluded that “infants
with mild Salmonella typhi enteritis do not require (antibiotic)
treatment.” Diarrhoea is a common feature of typhoid
fever in children, but is rarely associated with fluid
depletion. It should not, however, be inferred that the
finding of S typhi in a stool culture is of no clinical
importance; a positive stool culture, even in a healthy
contact, is often followed by a typical septicaemic illness
seven to 10 days later. Typhoid fever is usually a milder
disease in children than in adults, but life threatening
complications and even deaths have been reported,
especially among young, malnourished infants. The use
of antibiotics has resulted in a considerable reduction in the
morbidity and mortality of typhoid fever; thus treatment
of all cases of acute S typhi infections seems to be
indicated.

According to Chin et al the duration of the carrier state
of S typhi is not shortened by treatment with antibiotics. In
addition, chloramphenicol probably does not shorten the
carriage time of S typhi in treated patients. The problem is
that the reference cited by Chin et al to support this
statement is not relevant. The study mentioned was carried
out among children suffering from uncomplicated, non-
bacteraemic gastroenteritis caused by salmonella strains
other than typhi and paratyphi, an entity totally different
from typhoid fever.

P Yagupsy
Department of Paediatrics,
Ben-Gurion University of the Negev,
Beer-Sheva, Israel

References
1979;8:715–35.