Jennings, and
urea
That
Neurol.
J.
plasma
volume
of
the
nephrectomized
not
due
who
dye
operation
neurosurgical
indicated
and
most
implicated
by
Javid
(1)
fall
account
in
increase
not,
however,
volume
rises
in
some
(1919),
is
been
known,
but
that
the
effect
of
hypertonic
urea
is
due
to
this
diuretic
action
has
been
shown
on
nephrectomized
monkeys
(Javid
and
Anderson,
1959b).
It
has
also
been
shown
that
the
plasma
electrolyte
levels
do
not
change
appreciably
(Garvin,
Jennings,
and
Gesler,
1959).

Two
explanations
have
been
put
forward
to
account
for
the
shrinking
action
of
urea
on
brain
the
brain
bulk
in
intracranial
operations
and
to
lower
intracranial
and
intraocular
pressure
(Javid,
1958a
and
b,
1959).
That
urea
is
a
primary
diuretic
substance
has
long
been
known,
but
that
the
effect
of
hypertonic
urea
is
due
to
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action
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been
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Two
explanations
have
been
put
forward
to
account
for
the
shrinking
action
of
urea
on
brain

Several
publications
in
recent
years
by
Javid
and
his
colleagues
have
reported
on
the
use
of
hypertonic
urea
solutions
to
reduce
the
brain
bulk
in
intracranial
operations
and
to
lower
intracranial
and
intraocular
pressure
(Javid,
1958a
and
b,
1959).
That
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is
a
primary
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substance
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is
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not
change
appreciably
(Garvin,
Jennings,
and
Gesler,
1959).

Two
explanations
have
been
put
forward
to
account
for
the
shrinking
action
of
urea
on
brain

greater
than
could
be
accounted
for
even
had
all
the
water
been
removed
from
brain
and
cerebrospinal
fluid
and
prompted
us
to
question
the
blood-brain
barrier
explanation.
To
elucidate
the
point
a
small
series
of
experiments
in
dogs
was
performed
with
hypertonic
urea
infusions
and
the
results
are
presented.

Material
and
Method

The
plasma
volume
of
three
dogs
was
estimated
by
measuring
the
dilution
of
Evans
blue
dye.
Urevert
(30% urea
in
10% invert
sugar)
was
infused
intravenously,
1.5
g./kg.
dog
(Javid
and
Anderson,
1959a).
Blood,
muscle,
and
adrenal
samples
were
taken
before,
and
at
five,
10,
and
15
minutes
after
infusion
of
the
Urevert,
up
to
55
minutes,
and
urea,
nitrogen,
and
water
content
determined.
Muscle
and
adrenal
urea
were
determined
by
homogenising
the
tissue,
after
weighing
with
a
measured
volume
of
water,
centrifuging
it,
and
measuring
the
urea
content
of
the
supernatant
tissue
fluid.
Urine
urea
and
urine
flow
rate
were
determined
on
samples
from
an
indwelling
urethral
catheter.
The
femoral
artery
and
vein
were
cannulated
and
blood
pressure
changes
observed
manometrically.

Results

The
results
are
shown
graphically
in
Fig.
1,
where
the
rise
in
plasma
volume
is
expressed
as
a
percentage
of
the
initial
value.
The
absolute
values
for
plasma
volume
are
given
in
Table
I.
The
rapid,
initial
rise
in
plasma
urea
and
its
subsequent
rate
of
fall
is
paralleled
by
the
rapid
initial
rise
in
plasma
volume
and
its
subsequent
fall.

<table>
<thead>
<tr>
<th>TABLE I</th>
<th>ABSOLUTE INCREASES IN PLASMA VOLUME</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dog No. 3 (22 kg.)</td>
<td>Dog No. 4 (18 kg.)</td>
</tr>
<tr>
<td>Initial plasma volume (ml.)</td>
<td>1,730</td>
</tr>
<tr>
<td>Maximum increase in plasma volume after urea (ml.)</td>
<td>910</td>
</tr>
</tbody>
</table>

148
The haematocrit curve has been inserted since there was a considerable discrepancy in the rise in plasma volume calculated from the haematocrit, and the absolute rise determined by the Evans blue method, being much greater in the latter. The muscle urea will be seen to rise as the plasma urea falls, indicating that urea is entering muscle from plasma fairly quickly. In the first two dogs brain was sampled only at the end of the experiment, but it can be seen from brain urea levels that urea was also entering brain from plasma fairly quickly. The curves for muscle water and muscle nitrogen are best interpreted in conjunction with the curve for muscle urea. In dogs 3 and 5, as muscle urea rose, water rose and nitrogen fell. In dog 4 the relationship is less clearly seen.

The infusion in dog 3 produced a considerable diuresis. In dog 4 trouble with the catheter prevented full determinations, although the low urea concentration of the urine sample at the end of the experiment suggested that a diuresis had taken place. In dog 5 there was a very pronounced reduction in the flow of urine, the urine urea rose, and laparotomy at the conclusion of the experiment confirmed that the bladder was empty.

The lack of any continuous recording of arterial and venous pressures proved to be a disappointing omission where the time factor counted in such
very short intervals. It was clear, however, that the central venous pressure fell to the initial level and that the arterial pressure dropped during this period, then returned to pre-urea levels. These changes conform to the known pattern of blood pressure changes after infusion of a concentrated electrolyte solution (Evans, 1930) but the failure to correlate them accurately in time with the other changes precludes any conclusion being based upon them.

Discussion

The absolute increase in plasma volume was of such a magnitude as to suggest a general withdrawal of fluid from body tissues. The figures for plasma urea, muscle urea, muscle nitrogen, and muscle water showed that water was leaving muscle and entering plasma so long as urea was more concentrated in plasma than in muscle and that when urea began to enter muscle in appreciable amounts water returned to muscle. It was apparent that urea was also entering brain at much the same rate and to the same degree as it was entering muscle, and that presumably a generalized blood-tissue osmotic gradient obtained. The deceptively large reduction in brain bulk seen when urea is infused in neurosurgical cases we would put down to the existence of a blood-brain barrier after the removal of a blood-brain barrier after the infusion of hypertonic urea and to postulate that a generalized blood-tissue osmotic gradient prevails.

In future experiments it is hoped to show to what extent changes occur in the volume of interstitial fluid and in plasma osmotic pressure. In these calculations the volume of solutes was neglected and in future it would be better to express the changes in water in the fluid compartments in terms of true water. The figure really required is the volume of plasma water not of plasma. A rise in blood urea of 327 mg. % represents a rise of 54.5 mOsm. The normal osmolar value for mammalian plasma being of the order of 289 mOsm, this represents a rise of 18.9%. Except in one dog when it was 20%, the increase in plasma volume was much greater than this which suggests that when water enters the extracellular fluid from cells it carries with it other solutes, presumably to maintain equilibrium between normal constituents in cell water and extracellular fluid.

The striking reduction in urine flow after urea infusion in one dog is attributed to renal haemodynamic factors peculiar to the dog.

The disparity between the haematocrit and absolute plasma volume is attributed to the release of red cells into the circulation from depots such as the spleen.

Summary and Conclusions

Three dogs were infused with hypertonic urea solution (Urevert). Determinations of water and urea changes in plasma, muscle, and brain were made. ("Water" in this context is used rather loosely as pointed out in the discussion.)

It is concluded that Urevert has a powerful and transitory effect in increasing plasma volume, and that this effect is caused by the production of a generalized blood tissue osmotic gradient and the consequent removal of water equally from different tissues.

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REFERENCES


SOME EXPERIMENTAL OBSERVATIONS ON THE ACTION OF INTRAVENOUS HYPERTONIC UREA IN DOGS, WITH PARTICULAR REFERENCE TO PLASMA VOLUME AND TISSUE UREA CHANGES

Shedden Alexander, J. C. Eaton and H. J. Freedman

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