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Use of Bromide Electrodes for Rapid Screening of Elevated Bromide Concentrations in Biological Fluids

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Bromide determination in biological fluids by standard methods is either time consuming or requires expensive equipment (1, 2, 3, 4). Ion sensitive electrodes have rarely been used to determine bromide concentration in biological fluids. The procedure suggested by *Degenhart* et al (5) seems to be very accurate, but is time consuming and requires at least 2 samples from each patient. Furthermore an individual calibration curve has to be calculated for each patient by standardized bromide additions.
The bromide concentration in the serum of normals is below 0.1 mmol/l (6) and may reach values above 40 mmoles/l in patients with bromide intoxication (7). These concentrations are measurable with bromide electrodes (8). Bromide is liberated during the metabolism of bromoureide hypnotics; a review of bromoureide metabolism has been given by *Beyer* (9). Thus, it should be possible to detect the chronic abuse of bromide as well as of bromoureides with the same method.

Methods

Bromide-sensitive solid state $AgBr/Ag_2S$ electrodes from Orion (Cambridge, Mass., USA) and from Forschungsinstitut Meinsberg (DDR) were used together with an Ag/AgCl sleeve type reference electrode (90–01 Orion).
The reference electrode should show no response to any type of ion. This ideal situation can only be ensured, however, if the electrode solution (3 mol/l KCl) of the reference electrode can flow out freely. In this respect, the sleeve type electrodes, which we have used, are superior to any other type. Neither the stability nor the reproducibility were improved by an electrolyte measuring bridge; from this we conclude that possible diffusion potentials at the junction of the reference electrolyte and test solution are not a limiting factor in our measurements. The efflux from the reference electrode could, in theory, interfere with the measurements. However, since only about 0.2 µl of reference solution flows out in a 5 min measuring period, the chloride concentration of a 0.5 ml sample would increase by no more than 2 mmol/l; at physiological chloride concentrations of 105 mmol/l, this is negligible.
The measuring chain is independent of pH in the range pH 1–9. Readings were made in the expanded mV range of a digital pH meter (701, Orion) after 5 min of stabilization. After each measurement the electrodes were rinsed with dist. water and dried with Kleenex tissue. Between measurements the electrodes were left immersed in bromide solution (1 mmol/l). After each series of measurements the sensor area was polished with fine emery paper. Heparinized blood, plasma, serum, saliva or urine were measured at room temperature in plastic beakers. The minimum amount of fluid required was 0.5 ml. Calibrations were performed with standard bromide solutions (NaBr suprapur, E. Merck, Darmstadt) in dist. water before and after each series of the photometrical gold chloride method (10), which is fairly specific for bromide and does not measure bromoureides. Normal values were obtained from patients or volunteers without a history of bromide or bromoureide intake during the previous 2 months. They had bromide serum levels below the detection limit of the photometric method (0.5 mmoles/l). The values given are means and standard deviation (S.D.).

Results and Discussion

The calibration curves with pure bromide solutions were in agreement with published data (8). The slopes were – 58.0 mV/decade (Orion) and – 57.8 mV/decade (Meinsberg). 110 mmoles/l chloride (NaCl suprapur, E. Merck, Darmstadt) gave an apparent bromide concentration of 0.26 ± 0.03 (N = 10, Orion) or 0.28 ± 0.04 (N = 10, Meinsberg) mmoles/l. Thus, chloride interference corresponds to the values reported elsewhere (8). In the plasma of normals with added bromide (2–40 mmoles/l) the slopes were – 54.0 mV (Orion) and – 54.5 mV (Meinsberg) per decade. The apparent bromide concentration in plasma or serum of normals were 0.53 ± 0.13 (N = 82, Orion) and 0.53 ± 0.15 (N = 201, Meinsberg) mmoles/l. These values are higher than normal bromide concentrations. They may be partly explained by interference from chloride (s. above). Furthermore 0.033 mmoles/l cysteine (normal plasma concentration according to (11)) gave an apparent bromide concentration of 0.15 ± 0.02 (N = 10, Orion) and 0.13 ± 0.08 (N = 10, Meinsberg) mmoles/l. Thus, the high apparent bromide concentration in the serum or plasma of normals measured with electrodes can be explained mainly by interference from chloride and cysteine, which are present in normal plasma. From these results it is evident that elevated bromide concentrations can only be detected if they are above 1.0 mmoles/l. This value is outside the 3 S.D. range of both electrodes.
A slow drift to higher bromide values was observed with all biological fluids. With blood, plasma, serum or saliva of normals fairly stable readings were reached after 2–5 min. If the bromide concentrations were elevated, stabilization time was shorter. As shown in figure 1 the correlation between bromide concentration determined with electrodes and by the photometric method was good (serum or plasma from patients or volunteers after ingestion of bromide or bromoureides). To check the reproducibility serum samples from a severely bromide intoxicated patient and from a volunteer after ingestion of carbromal (1 g per day for several weeks) were divided into 10 parts and measured on different days. The photometrically determined bromide concentrations were 23.3 and 2.1 mmoles/l. With the first sample electrode measurements were 23.3 ± 1.6 (Orion) and 23.5 ± 1.7 (Meinsberg) mmoles/l, with the second one 3.4 ± 0.3 (Meinsberg) mmoles/l.
With *blood* from normals the apparent bromide concentrations measured by electrodes were 0.56 ± 0.10 (N = 34, Orion) and 0.57 ± 0.10 (N = 41, Meinsberg) mmoles/l. The correlation between electrode measurements in blood and the photometric bromide determination in the plasma of patients after the ingestion of bromide or bromoureides was satisfactory (correlation coefficients 0.981 and 0.985, 44 pairs). Thus electrode measurements in blood give a rather good estimate of bromide concentration in plasma.

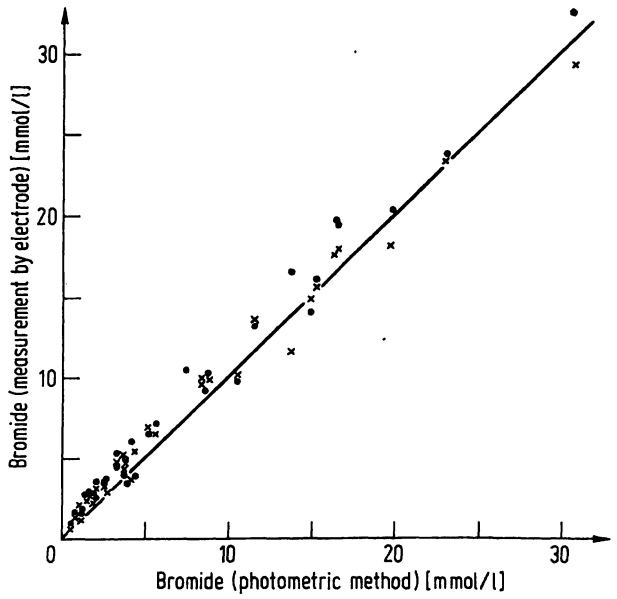

Fig. 1. Comparison of bromide determination performed with bromide sensitive electrodes and by a photometric method. Serum or plasma from patients or volunteers with elevated bromide concentrations were measured with both methods.

× = Orion electrode, 31 pairs, r = 0.994
• = Meinsberg electrode, 35 pairs, r = 0.992

With *saliva* from normals the apparent bromide concentrations with electrodes were 0.22 ± 0.13 (N = 91, Orion) and 0.24 ± 0.16 (N = 89, Meinsberg). The molar concentration ratio bromide/chloride in saliva is higher than in plasma (12). Thus, in cases with low bromide levels the electrode measurement in saliva may be preferred. On the other hand, halide concentration in saliva depends on the flow rate (12). Therefore, bromide measurements in saliva give only a rough estimate of the severity of bromide intoxications.

In *urine* the molar concentration ratio bromide/chloride is lower than in plasma. Furthermore the bromide excretion depends on chloride intake. The concentration of interfering substances in urine (e.g. iodide or compounds with free SH-groups) can be much higher than in plasma. For these reasons bromide determinations in urine with electrodes are expected to be unreliable. This is reflected by high and variable values in the urines of normals: 0.80 ± 0.36 (N = 15, Orion) and 0.71 ± 0.41 (N = 15, Meinsberg) mmoles/l. Additionally we observed severe stirring effects and sometimes extreme drifting during measurement in urine. Thus, electrodes are considered unsuitable for direct bromide determination in urine.

Acute poisoning with bromoureides cannot be diagnosed with bromide electrodes since they do not respond to covalently bound bromine. A serum sample drawn from a patient 3 h after attempted suicide with carbromal contained 0.6 mmoles/l bromide calculated from an electrode reading (0.5 mmoles/l photometrically) which is within the normal range (mean ± 3 S.D.) of electrode measurements in serum. After 24 h the concentration was 1.6 mmoles/l (1.2 mmoles/l photometrically). Obviously it was more than 3 h before enough bromide was liberated from carbromal to yield detectable bromide levels. The slow metabolic degradation of bromoureides has been described elsewhere (9). Determination of bromide concentration with electrodes in biological fluids can rapidly reveal elevated bromide concentrations in patients. For more exact, quantitative results one of the standard methods should also be used. Bromide concentrations below 1 mmol/l, which could not be detected with electrodes (due to the presence of chloride and cysteine in normal plasma), are of no clinical relevance (13).

Bromoureide- and bromide-containing drugs are available without prescription in the Federal Republic of Germany. Abuse of these drugs is a significant problem (14). Thus, a detection method suitable for use on the ward or in the outpatient department may help to reveal cases with elevated bromide levels in body fluids. The simple procedure of bromide determination with electrodes described in this paper yields results within a few minutes.

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