DYNAMIC ASPECTS OF ELECTROLYTE AND WATER TRANSFERS IN HUMAN BLOOD AFTER MORPHINE

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THE FIRST REPORT on the influence of anaesthetics on acid-base status goes back to Austin and Jonas in 1917.¹ It was followed by a number of papers concerned with the interrelationship between anaesthesia and electrolyte metabolism.²⁻¹¹ However, only Austin and Jonas reported findings obtained in humans.

With our increasing knowledge on the importance of electrolyte and water balance for the course of physiological processes and the restitution after disease and surgery, studies have also been extended to the pre- and post-operative periods; they promoted insight into the effects of surgical trauma in its entirety. Although these investigations were carried out particularly by paediatricians, physiologists, internists, and surgeons, anaesthesiologists too made their contribution to this field. Nearly fifty years after the initial investigations, the effects of halothane,¹²⁻¹⁵ chloroform,¹² and cyclopropane^{15,16} on plasma electrolytes and acid-base equilibrium were re-examined using newer methods.

Invaluable as these findings are, they cannot represent solely the effect of the drug used. A different number of variables (e.g. diverse premedications, different depths of anaesthesia, type and extent of surgery) seem to exclude such an assumption. Already the effect of a morphine premedication is an open question in this respect. With exception of Cl^- and HCO_3^- ^{17,18} there are no reports on the influence of morphine on electrolyte and water balance.

The aim of the present study is therefore to evaluate the effect of morphine on the transfer of water and electrolytes between cells and extracellular space in order to differentiate the influence of premedication from that of anaesthetic agents.

MATERIAL AND METHODS

The present investigation was conducted in 23 male patients at the Surgical Division, Robert Roessle Klinik, German Academy of Sciences, Berlin-Buch (GDR). In this group, 21 patients suffered from circumscribed, mainly neoplastic lung diseases without respiratory or metabolic disorders affecting the acid-base balance; two patients had peripheral tumour. The age of these volunteers ranged from 32 to 71 years (mean of 56 years); their body surface was between 1.6 and 2.0 square metres.

All results were obtained in fasting patients between 8 and 10 A.M. During this interval, diurnal variations in electrolyte concentrations and acid-base balance should be small, unidirectional, and comparable in all experiments. All patients were recumbent and had no physical effort before or during investigation.

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After local analgesia the right femoral artery was punctured and an indwelling polyethylene catheter introduced. Blood samples were taken intramuscularly before and one hour after 12 mg. morphine hydrochloride per square metre body surface, using all glass syringes or special syringes made from Piacryl P®.¹⁹ The dead space was filled bubble-free with 3 per cent calcium heparinate in 5 per cent dextrose. P_{aO_2} , pH, and actual HCO_3^- of arterial plasma were obtained at 38°C. by the method of Siggaard-Andersen *et al.*^{20,21} using an Astrup Micro Equipment AME 1b (Radiometer, Copenhagen). Each value was based on duplicate measurements. For the estimation of intracellular and plasma electrolytes, anaerobically separated erythrocytes and plasma were used;¹⁹ the blood was spun at 5000 r.p.m. or a relative centrifugal force of 3400 g for 30 minutes. With this procedure the trapped plasma amounted to 2.64 ± 0.66 per cent.

The intracellular and the plasma Na^+ and K^+ concentrations were measured by means of a Model III flame photometer (VEB C. Zeiss, Jena), using interference filters Na 59 and K 77. Intracellular cations were estimated after haemolizing the red blood cells in ion-free water. Corrections were made for the interference of haemoglobin iron with sodium ions. Chloride was measured in plasma or haemolysates by potentiometric titration. Formation of silver proteinate was prevented by an admixture of 50 per cent chloride-free acetic acid. The binding of silver ions by SH-groups of haemoglobin was prevented by NEM inhibition.

The water content of plasma and erythrocytes was estimated by lyophilization, applying a mercury diffusion pump. Lyophilization was stopped after a vacuum of 10^{-4} mm. Hg was reached.

Haemoglobin concentration was measured as cyan-haemoglobin using Acuglobin plus aculte (Ortho Pharmaceutical Corp., Raritan, New Jersey) as a standard. This concentration was converted from gm. per cent into mEq./L. by multiplying by 0.5988. The haematocrit was ascertained in Wintrobe tubes applying 3400 g for 30 minutes. Red cell counting (RBC) was performed using a Neubauer haemocytometer with Thoma net. Donnan factors for Cl^- and HCO_3^- were calculated by division of plasma concentration by intracellular concentration. The intracellular pH of erythrocytes was calculated by applying the formula $pH_e = pH_p + \log r$. The intracellular bicarbonate concentration was computed employing the formula

$$[HCO_3^-]_e = \text{antilog} [0.0262 \cdot P_{aCO_2}] + [pH_e - 6.105].^{22}$$

The significance of the results were determined by the *t*-test.

RESULTS

1. Effects on plasma ions

The action of morphine caused a mean fall in pH from 7.405 to 7.383. This shift to the acid side was explained by an average increase of P_{aCO_2} of 1.5 mm. Hg (i.e. from 36.9 to 38.4 mm. Hg). These P_{aCO_2} volumes are 1 to 2 mm. Hg lower than the "alveolar" end-expiratory CO_2 tensions measured by Eckenhooff *et al.*²³ after morphine sulfate. A difference of 1.9 mm. Hg between P_{aCO_2} and P_{ACO_2} was also reported as a result of the different methods of measurement used.²⁴

Under normal conditions an increase of bicarbonate and a coincidental rise of carbonic acid in the proportion of 20:1 should not change the pH. On the contrary, the actual bicarbonate fell from 23.16 to 22.78 mEq./L. This bicarbonate deficit will be discussed later.

Whereas the HCO_3^- content fell, in disagreement with the Hamburger phenomenon, the plasma chloride showed the expected effect. The chloride fell on the average from 100.66 to 99.54 mEq./L.

Under the conditions of this respiratory acidosis a small rise in plasma potassium (from 4.08 to 4.32 mEq./L.) could be observed similar to that reported by Elkinton *et al.*²⁵ after inhalation of CO_2 enriched gas mixtures. The plasma sodium, however, was decreased from 137.63 to 135.01 mEq./L.

The water content of plasma rose from 10075.1 to 10337.9 gm./kg. dry substance. This finding is in agreement with results of Eichelberger and Hastings²⁶ and the thermodynamic law that there is no ionic transfer without simultaneous water movement.

2. Effects on red blood cells

Under the effect of morphine there was a fall in red cell pH from 7.224 to 7.213 units. This intracellular increase of hydrogen ion concentration was accompanied by a chloride transfer of 1.07 mEq./L. from the extracellular space into the red cells, i.e., a mean change of Cl^- content from 66.27 to 67.34 mEq./L.

Although a decrease in actual cell HCO_3^- should be expected according to the Hamburger phenomenon, a migration of bicarbonate ions into red cells was observed. The mean change amounted to +0.227 mEq./L. and was opposed by a plasma HCO_3^- deficit of -0.381 mEq./L. The mean values of cellular bicarbonate were 12.71 mEq./L. before and 12.94 mEq./L. one hour after morphine.

Both sodium and potassium ions were diminished. The cellular Na^+ concentration fell from 23.07 to 22.17 mEq./L. and the K^+ ions were reduced from 81.51 to 80.03 mEq./L.

In contrast to the plasma, the intracellular water content decreased from 2086.8 to 2075.0 gm./kg. dry substance.

3. Alteration of whole blood characteristics

As a consequence of the water transfer into the extracellular fluid space the red cell count fell from 4.24 to 4.11 million/mm.³. The simultaneous drop of the haemoglobin concentration from 8.02 mEq./L. to 7.82 mEq./L. and of the haematocrit from 41.3 to 40.5 per cent are likewise signs of a haemodilution.

A rise in Donnan factors was the consequence of a transfer of Cl^- and HCO_3^- from plasma into red cells. The factor ' HCO_3^- ' rose from 0.548 to 0.568 and ' Cl^- ' rose from 0.658 to 0.676.

The mean values, standard deviations, differences, and statistical significances are summarized in Table I.

DISCUSSION

Although there are several papers discussing the effects of morphine,^{27,28} only a few deal with its effect on electrolytes^{18,29-31} and these report mainly on chlo-

TABLE I

MEAN VALUES, STANDARD DEVIATIONS, MEAN CHANGES, AND P VALUES OF DIFFERENT ELECTROLYTES, ACID-BASE PARAMETERS, WATER, AND CONSTITUENTS OF HUMAN ARTERIAL BLOOD BEFORE AND ONE HOUR AFTER THE ADMINISTRATION OF 12 MG. MORPHINE PER SQUARE METER BODY SURFACE

	Red blood cells		Plasma	
	before	after	before	after
Na ⁺ (mEq./L.)	$\bar{x}$ 23.07 s ± 4.86 Δ 0.02 p 0.02	22.17 ± 2.93 -0.901	137.63 ± 3.47 -2.62 0.02	135.01 ± 3.80
K ⁺ (mEq./L.)	$\bar{x}$ 81.51 s ± 7.43 Δ 0.01 p 0.01	80.03 ± 6.29 -1.48	4.08 ± 0.26 +0.245 0.01	4.32 ± 0.30
Cl ⁻ (mEq./L.)	$\bar{x}$ 66.27 s ± 2.75 Δ 0.01 p 0.01	67.34 ± 2.18 +1.07 0.01	100.66 ± 3.01 -1.12 0.01	99.54 ± 3.24
HCO ₃ ⁻ (mEq./L.)	$\bar{x}$ 12.71 s ± 0.98 Δ 0.01 p 0.01	12.94 ± 0.98 +0.227 0.01	23.16 ± 1.48 -0.381 0.05	22.78 ± 1.54
H ₂ O (ml./kg. dry substance)	$\bar{x}$ 2086.8 s ± 66.5 Δ 0.05 p 0.05	2075.0 ± 91.2 -11.8 0.05	10075.1 ± 503.7 +262.9 0.01	10337.9 ± 618.5
pH	$\bar{x}$ 7.224 s ± 0.01 Δ 0.01 p 0.01	7.213 ± 0.01 -0.01 0.01	7.405 ± 0.01 -0.022 0.01	7.383 ± 0.01
Whole blood				
	before		after	
	$\bar{x}$		$\bar{x}$	
RBC count ($\times 10^6$ /mm. ³)	$\bar{x}$ 4.24 s ± 0.36 Δ -0.123 p 0.01		4.11 ± 0.41	
Hb (mEq./L.)	$\bar{x}$ 8.02 s ± 0.85 Δ -0.204 p 0.01		7.82 ± 0.77	
HCO ₃ ⁻	$\bar{x}$ 0.548 s ± 0.03 Δ +0.019 p 0.01		0.568 ± 0.02	
Hct (%)	$\bar{x}$ 41.3 s ± 4.61 Δ +0.84 p 0.01		40.5 ± 4.04	
Cl ⁻	$\bar{x}$ 0.658 s ± 0.02 Δ +0.018 p 0.01		0.676 ± 0.02	
Paco ₂ (mm. Hg)	$\bar{x}$ 36.9 s ± 3.94 Δ +1.5 p 0.01		38.4 ± 3.0	

ride and bicarbonate ("alkali-reserve") changes. Furthermore, only the studies by Gauss³⁰ and Schoen¹⁸ are concerned with man. The species differences of morphine effects³² indicate that findings in animals should probably not be applied to man.

But also findings in man are not always comparable. While Schoen¹⁸ reported a shift of -0.1 to 0.2 units in venous blood after medication of 5 to 20 mg. of morphine hydrochloride, in our cases a shift of only -0.022 units in arterial blood was found. Schoen did the pH measurement electrometrically; the difference can therefore be explained only by the source of blood. Since venous blood is in equilibrium with the tissues drained, it represents their total buffering capacity affected by some metabolic and respiratory factors. Therefore only arterial blood is suitable for electrolyte or acid base studies.

The concomitant fall in pH and increase of P_{CO_2} under morphine is also evident from investigations of Loeschcke *et al.*³³ and Eckenhoff *et al.*²³ Both groups, however, measured the "alveolar" end-expiratory CO_2 tension. That value differs, according to Lerche *et al.*,²⁴ by $+1.9$ mm. Hg from arterial P_{CO_2} .

Such a difference is valid only for Lerche's group, which averaged 22 years of age: Ulmer and Reichel³⁴ found that difference is dependent on age. Correcting the findings of Loeschcke by Ulmer's age-dependent alveolo-arterial CO_2 differences, a good agreement was found with the mean change of $+1.5$ mm. Hg P_{aO_2} observed by us.

According to van Slyke *et al.*³⁵ the Donnan factor r is equal to the quotient of intracellular and extracellular anions $[An^-]_i/[An^-]_p$ or, with reference to the anionic equivalence of haemoglobin, equal to $1 - ([Hb^-]/2[An^-]_p)$. In this expression the importance of haemoglobin for the distribution of diffusible anions and cations is emphasized. The concentration of Hb^- , however, is a function of pH and decreases with a falling pH. Consequently the quotient becomes smaller and r greater in acidosis. A rise in r means, therefore, an increase of cellular anions (other than Hb^-) or a decrease of plasma anions. In our experiments the HCO_3^- content of the red blood cells rose and changed from 12.71 to 12.94 mEq./L., corresponding to $'HCO_3^- = 0.548$ before and 0.568 after morphine.

In regard to bicarbonate, it is obvious that the rise in $'HCO_3^-$ is caused not only by an increase of red cell bicarbonate but also by the fall in plasma bicarbonate from 23.16 to 22.78 mEq./L.

Bicarbonate deficits in respiratory acidosis have been reported up to date only twice,^{36,37} and in each case under high CO_2 tensions. The reports of Schoen¹⁸ and Hollo *et al.*¹⁷ on a fall in alkali reserve after morphine are of lesser importance, because whole blood was not used for the estimations. Their values are neither actual bicarbonate nor standard bicarbonate and thus not suitable to assess transfers.

When comparing the molal changes in bicarbonate concentration, a cellular gain of $+0.33$ mEq./kg. H_2O is opposing a plasma loss of -0.476 mEq./kg. H_2O . It seems to be likely, therefore, that still other body compartments (interstitial fluid, muscles, etc.) are taking part in the redistribution of ions. In addition to such a transfer into other body compartments, an increase of other anions than HCO_3^- or a fall in the plasma cation concentration would help to explain a

bicarbonate deficit. The result of both or a change in anion or cation concentration could lead to a bicarbonate value lower than that corresponding to pH and P_{aCO_2} .

Applying a formula of Hastings *et al.*,³⁸ it is obvious that a transfer of multi-valent inorganic phosphate ions into the extracellular space in acidosis influences the change of r . Such increase in manifold negative ions in extracellular fluid is at the expense of HCO_3^- ions and could explain their deficit. These theoretical considerations are supported by reports on the behaviour of organic acid-soluble phosphates under different states of acidosis.³⁹⁻⁴² These investigators found a fall in organic phosphate ions in cells and an increase of an organic phosphate in plasma.

Although these findings apply strictly speaking only to metabolic acidosis, an analogous application to respiratory acidosis seems to be practicable in the light of a report of Fanestil *et al.*⁴³ They found with rising PCO_2 an increase of ATPase activity in mitochondria, accompanied by an increasing amount of an organic phosphate.

Like bicarbonate, chloride, as a diffusible anion is subject to the Donnan principle. A morphine dependent shift of chlorides into red blood cells has already been reported by Schoen,¹⁸ but unfortunately only for venous blood. In our experiments we found an increase of red blood cell (RBC) chlorides from 66.27 to 67.34 mEq./L. (mean $\pm$ 1.07 mEq./L.). The plasma chlorides fell by -1.12 mEq./L. Such good agreement per litre of RBC and plasma respectively shows that chlorides are obviously not redistributed between blood and other fluid compartments. The Donnan factor changed from 0.658 to 0.676.

For the shift of chloride ions from plasma into RBC the same interrelations apply as for bicarbonate. These apply to the dependence of concentration and ionic equivalence of diphosphoglyceric acid and Hb-^{40,44} as well as to PCO_2 and pH.^{45,46}

While the *in vitro* experiments of Hamburger,⁴⁶ Guerber,⁴⁵ and Henderson⁴⁷ showed a water shift into the red blood cells with elevated CO_2 tensions, this effect is not seen *in vivo* in morphine-induced respiratory acidosis. Here water shifts from cells to plasma.

Contrary to conditions in the test tube, there is no "closed system" *in vivo*, but an equilibrium is also possible between other fluid spaces and blood. The change in the water content from 2086.8 to 2075.0 gm. H_2O /kg. dry substance in red blood cells and from 10075.1 to 10337.9 gm. H_2O /kg. dry substance in plasma makes a new equilibrium with other systems more likely. A gain of 262.9 gm. H_2O /kg. d.s. in plasma and a loss of 11.8 gm. H_2O /kg. d.s. in RBC could not be explained otherwise. This assumption is in agreement with reports by Eichelberger and Hastings,²⁸ who found a water loss of the musculature in respiratory acidosis; also, Malorny⁴⁸ found hydraemia in CO_2 intoxication. As Williams⁴⁹ did in morphine addicts, we consistently found a fall in haematocrit of 0.84 per cent. This percentage shows a statistical significance of $p < 0.01$. Corresponding to this fall in haematocrit the RBC count decreased from 4.24 to 4.11 million/mm.³ whole blood, which represents a fall in Hb concentration from 8.02 to 7.82 mEq./L.

Applying the same proportions between control haematocrit and RBC count to

the values after morphine, an RBC count of 4.11 million should correspond to a haematocrit of 40.03 per cent. The observation of a haematocrit of 40.5 per cent after centrifugation is in good agreement with this.

As there are no investigations known to us dealing with cation transfers under morphine, parallels can only be drawn regarding experimental respiratory acidosis.

Elkinton *et al.*²⁵ found in man, and Malorny⁴⁸ in dogs and rabbits, an increase in plasma potassium during respiratory acidosis. Elkinton and co-workers used a carbon dioxide concentration of 7.5 to 7.7 per cent, which corresponds to a P_{aCO_2} of 59 mm. Hg,⁵⁰ and obtained an insignificant increase of 0.1 mEq./L. K^+ in plasma.

In our experiments the potassium rose from 4.08 to 4.32 mEq./L. plasma. This increase of 0.245 mEq./L. is statistically significant ($p < 0.01$). On the other side, there was a mean loss of 1.48 mEq./L. K^+ from red blood cells. Assuming a mean RBC relation of 30.3 ml./kg. body weight,⁵¹ a loss of 3.13 mval. K^+ could be expected in a 70 kg. man, to be dissolved in a mean plasma volume of 41.1 ml./kg. body weight. In the case of a plasma volume of 2.877 litres, that distribution should result in an increase of 1.08 mEq./L. As the dilution of plasma potassium is not explained by the water gain of 2.6 per cent alone, a redistribution into other body compartments must be assumed. Indeed, Malorny⁴⁸ found a shift from plasma into muscle tissue changing the CO_2 tension from 22 to 35 mm. Hg.

Due to the very low sodium content of RBC the loss amounted to only 0.9 mEq./L. ($p < 0.02$). But in plasma the sodium concentration was likewise diminished by 2.62 mEq./L. This cannot be explained by haemodilution alone and seems to fit into the findings of Malorny⁴⁸ showing a Na^+ shift into musculature as a cause of hyponatremia in respiratory acidosis.

SUMMARY

After the intramuscular injection of clinically used doses of morphine, arterial plasma and corpuscular constituents of human arterial blood were separated under actual conditions by means of a new method. Whole blood as well as red blood cells and plasma were used for dynamic studies of acid-base balance, red blood cell counts, haematocrit, concentrations of anions and cations, the water content of cells and plasma, and the Donnan equilibrium of bicarbonate and chloride.

Under the maximal effect of 12 mg. morphine/m.² body surface we found a small acidification of the arterial blood. The pH of the true plasma decreased on the average from 7.405 to 7.383 and the P_{aCO_2} rose by 1.5 mm. Hg. This slight change of acid-base equilibrium, however, led, under actual conditions, to a loss of Na^+ , K^+ , and water from the red blood cells and a simultaneous gain of potassium and water in plasma. On the other hand Na^+ was also found to be diminished in plasma. The resulting deficit is discussed.

The chloride and bicarbonate contents of red blood cells increased. This transfer was not fully compensated for and, accordingly, a plasma bicarbonate deficit arose. The Donnan coefficient of chloride increased by 0.018 and that of bicarbonate by 0.019 on the average.

The redistribution of water between the intracellular space and plasma led to a haemodilution which decreased the RBC count, haematocrit, and haemoglobin content.

RÉSUMÉ

Au moyen d'une méthode nouvelle il a été possible de séparer, en des conditions actuelles, le plasma artériel et des constituants corpusculaires du sang humain, après l'injection intramusculaire de doses cliniques de morphine. Le sang total comme les globules rouges et le plasma ont été employés pour des études dynamiques de l'équilibre acide-base, comptage de globules rouges, hématocrite, concentration d'anions et cations, contenu d'eau des globules et du plasma, et équilibre de Donnan du bicarbonate et chlorure.

Dans l'effet maximum de 12 mg. de morphine par m.² de superficie corporelle, nous avons constaté une légère acidification du sang artériel : le pH du plasma diminua en moyenne de 7.405 à 7.383, et le P_{aCO_2} s'éleva de 1.5 mm. Hg. Cette légère modification de l'équilibre acide-base a provoqué une perte de sodium, potasse et eau dans les globules rouges et une augmentation simultanée de potasse et eau dans le plasma. On a par contre également observé que le sodium diminuait aussi dans le plasma. La question du déficit est discutée.

Le chlorure et bicarbonate des globules rouges a augmenté. Ce transfert n'a pas été entièrement compensé, provoquant pourtant un déficit de bicarbonate dans le plasma. Les coefficients de Donnan du chlorure et bicarbonate ont augmenté, en moyenne, respectivement, de 0.018 et 0.019.

La redistribution de l'eau entre l'espace intracellulaire et le plasma a provoqué une hémophilution, diminuant le comptage des globules rouges, l'hématocrite et l'hémoglobine.

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