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Variable Selectivity of the Hitachi Chemistry Analyzer Chloride Ion-Selective Electrode Toward Interfering Ions

TAO WANG,^{1,2} ELEFTHERIOS P. DIAMANDIS,^{2,3} ALLAN LANE,⁴ and ANDREW D. BAINES^{1,2}

¹Department of Clinical Biochemistry, Toronto General Division, The Toronto Hospital, 200 Elizabeth Street, Toronto, Ontario M5G 2C4, ²Department of Clinical Biochemistry, University of Toronto, 100 College Street, Toronto, Ontario M5G 1L5, ³Department of Clinical Biochemistry, Toronto Western Division, The Toronto Hospital, 399 Bathurst Street, Toronto, Ontario M5T 2S8, and ⁴Boehringer Mannheim Canada, 201 Boulevard Armand-Frappier, Laval, Quebec H7V 4A2, Canada

Chloride measurements by ion-selective electrodes are vulnerable to interference by anions such as iodide, thiocyanate, nitrate, and bromide. We have found that the degree of interference of these anions on the Hitachi chemistry analyzer chloride electrode varies from electrode to electrode and this variation can even occur within the same lot of membrane. This variation is not dependent upon the length of time the cartridge has been in the analyzer because no correlation existed between the usage time and the electrode response to interfering ions. Neither is this variation due to the deterioration of the electrode because all electrodes tested had calibration slopes within the manufacturer's specification. Our study, however, showed that even after repeated exposure to a plasma sample containing 2 mM thiocyanate, the chloride electrode was still able to accurately measure the chloride in plasma without thiocyanate, thus confirming that a carryover effect does not exist from a previous thiocyanate-containing sample.

KEY WORDS: chloride; ion selective electrode; interference; thiocyanate.

Introduction

In modern clinical biochemistry laboratories, sodium, potassium, and chloride are predominantly measured by ion-selective electrodes (ISE). Measurement of these electrolytes by ISE is simple, quick, accurate, inexpensive, and free of common interferences like turbidity, haemolysis, and bilirubin. However, the selectivity of the ISE toward the primary ion is not absolute and is expressed by the selectivity coefficient of the ISE that in turn depends on the ISE membrane composition. The poor selectivity of the chloride ISE toward various organic and inorganic anions is well documented despite the im-

provements in fabrication of chloride ISE (1). Selectivity coefficient ($K_{i,j}$) defines the ability of an ion-selective electrode to distinguish between the primary ion i and the interfering ion j in the same solution (2). The larger the value of $K_{i,j}$, the poorer the selectivity of the ISE toward the primary ion i in the presence of the interfering ion j . Many anions, such as I^- , Br^- , NO_3^- , SCN^- , etc., have $K_{i,j}$ well over 1 on most types of Cl^- ISEs (1). For example, $K_{Cl,I}$ and $K_{Cl,SCN}$ are 3.06 and 2.89, respectively, for a liquid/liquid ion-exchange Cl^- ISE using crystal violet-chloride. $K_{Cl,I}$ and $K_{Cl,SCN}$ are 5.37 and 5.88 for a solid/ion-exchange resin membrane Cl^- ISE containing both quaternary ammonium group and sulphonic group. Interferences of Cl^- ISE measurements by these ions (3-7) and some drugs (8) in clinical samples have also been reported.

The Hitachi analyzer chloride ISE has been the subject of several recent publications (7,9-10). Our study on the selectivity of Hitachi Cl^- ISE toward some interfering ions was prompted by erroneously elevated Cl^- results found in one of our patient's plasma. Our study demonstrated that I^- , SCN^- , NO_3^- , and Br^- ions erroneously elevated Cl^- reading on some of the Hitachi chemistry analyzer Cl^- ISE cartridges but the degree of interference varied from one electrode to the next, even within the same lot of membrane, and these variations were not dependent upon the length of time the cartridge had been in the analyzer.

Materials and methods

Chloride electrodes (Cat. No. 722-4013) were obtained from Boehringer Mannheim Canada (Laval, Quebec, Canada). This type of electrode, based on a liquid-liquid ion exchanger with quaternary ammonium salts, is used in all Boehringer Mannheim/Hitachi model 704, 717, 736, 737, 747, and 911 chemistry analyzers. The chloride electrode lots

Correspondence: Dr. Andrew D. Baines, Department of Clinical Biochemistry, The Toronto Hospital, Toronto General Division, 200 Elizabeth Street, Toronto, Ontario M5G 2C4, Canada.

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K42, H90, and K27 were used for this study. Electrodes K4269, H9086, and H9089 had been used for 2 weeks before the investigation, whereas electrodes K2702 and K2782 had been used for less than 3 days. Electrodes K4237 and O4015 were new at the time of this study.

All chemicals were analytical grade and purchased from BDH Inc. (Toronto, ONT, Canada).

Chloride in plasma was measured by Cl^- ISE on a Hitachi model 737 chemistry analyzer or by coulometric titration on a Fiske Chloro-O-Counter (Uxbridge, MA, USA), or by a disposable thin-film Cl^- ISE on a Kodak Ektachem 700 chemistry analyzer (Rochester, NY, USA). The ISE reagent for Hitachi chemistry analyzer was prepared at The Toronto Hospital. Many experiments were also repeated using BM diluent (Cat. #820638), BM internal reference (Cat. #836246), and BM KCl reference (Cat. #820639) obtained from Boehringer Mannheim. Thiocyanate was measured in protein-free filtrate of serum by reaction with ferric ions; the intensity of the colour was measured spectrophotometrically at 515 nm (11).

To compare the selectivities of BM/Hitachi chloride electrode, different amounts of sodium or potassium salts of iodide (I^-), thiocyanate (SCN^-), cyanide (CN^-), bromide (Br^-), thiosulphate ($\text{S}_2\text{O}_3^{2-}$), sulphate (SO_4^{2-}), bicarbonate (HCO_3^-), fluoride (F^-), or nitrate (NO_3^-) were dissolved in Hank's balanced salt solution (CaCl_2 anhydrous, 1.3 mM; KCl, 5.0 mM; KH_2PO_4 , 0.3 mM; $\text{MgCl}_2 \cdot 6\text{H}_2\text{O}$, 0.5 mM; $\text{MgSO}_4 \cdot 7\text{H}_2\text{O}$, 0.4 mM; NaCl, 138 mM; NaHCO_3 , 4.0 mM; Na_2HPO_4 , 0.3 mM; glucose, 5.6 mM). One hundred microliters of these solutions were added into 900 μL of pooled plasma to obtain final concentrations of interfering ions ranged from 0.5 to 10 mmol/L. Sodium nitroprusside was also spiked into the pooled plasma to give final concentrations from 1 to 20 mmol/L. The recovery of chloride was analyzed by linear regression (6,12) and the slope of the regression line was expressed as a fraction of unity. A fraction of unity is used to compare the extent of interference toward ISE in automated analyzers (7) and is defined as "mmol/L of electrolyte value contributed by each mmol/L of interfering ion." A fraction of unity, rather than the forementioned $K_{i,j}$, is generally used to compare the selectivity of ion-selective electrodes in clinical laboratories. The reason is that the electromotive force (EMF) or potential, required for the calculation of $K_{i,j}$ using a modified Nernst equation, is not readily available from the automated chemistry analyzers. In contrast, we can use the reported chloride concentrations directly to perform linear regression analysis.

Results

The patient under investigation was a 52-year-old female who had severe congestive heart failure due to end-stage ischaemic cardiomyopathy. During hospitalization, she received various medications including digitalis, diuretics, and vasodilators. After

being administered sodium nitroprusside (Niprid[®], Roche; 100–200 mg daily) for 5 days, she showed manifested signs of cyanide toxicity. Thiosulphate (2 g daily for 3 days) was given to treat her cyanide toxicity. Thiosulphate enhances the conversion of cyanide to the less toxic thiocyanate (Figure 1). As shown in Table 1, this patient's plasma chloride level was analyzed on two different Hitachi 737 analyzers and found to differ significantly. One cartridge was unaffected while the other displayed significant interference. Both the Ektachem and coulometric titration methods recovered the same chloride value as the unaffected Hitachi electrode (#2) and similar chloride values were obtained for both Hitachi electrodes in a thiocyanate-free sample (control plasma). Both plasma #2 and control plasma had normal sodium, potassium, and bicarbonate levels.

Clearly, an erroneously elevated response was obtained with one of the chloride ISE cartridges (K4269). To investigate what might have caused this false reading, we added various amounts of sodium nitroprusside and sodium salts of cyanide (CN^-), thiosulphate ($\text{S}_2\text{O}_3^{2-}$), and thiocyanate (SCN^-), respectively, to pools of human plasma and measured the chloride levels with different lots of Hitachi chloride cartridges. Because other anions such as iodide (I^-), bromide (Br^-), fluoride (F^-), nitrate (NO_3^-), bicarbonate (HCO_3^-), and sulphate (SO_4^{2-}) have been reported to interfere with the chloride measurement by ion-selective electrodes, they were also included in the study.

SCN^- , I^- , NO_3^- , and Br^- significantly elevated chloride readings (Figure 2, Table 2). Nitroprusside was also found to interfere with the Cl^- measurements, but in a nonlinear fashion (data not shown). However, we suspect that nitroprusside is unlikely to cause an appreciable interference when present in blood because its half-life is approximately one minute *in vivo* (13). We have thus excluded it in our assessment of the fraction of unity (Table 2). In comparison to the ISE, measurement of Cl^- by coulometric titration is less affected by the same interfering ions.

The interference in chloride measurement observed with lot K4269 in the patient plasma is probably due to SCN^- ions. The measured SCN^- levels were 0.8 and 2.1 mmol/L on two separate occasions (see Table 1), which is equivalent to 15 and 40 mmol/L of chloride when using the fraction of unity value of 18.93. These calculated values are very

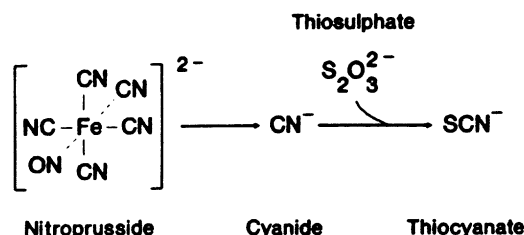


Figure 1 — Conversion of nitroprusside to cyanide and thiocyanate after thiosulphate treatment.

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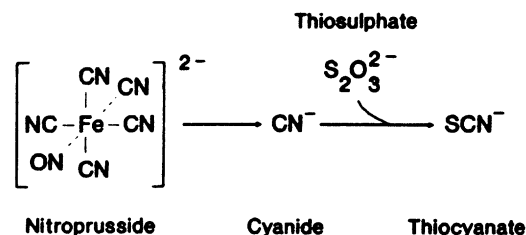


Figure 1 — Conversion of nitroprusside to cyanide and thiocyanate after thiosulphate treatment.

INTERFERENCE OF CHLORIDE MEASUREMENT

TABLE 1
Thiocyanate and Chloride Values

Analyte	Thiocyanate or Chloride (mmol/L)		
	Plasma #1 ^a	Plasma #2 ^a	Control Plasma
Thiocyanate ^b	0.8	2.10	0.00
Chloride			
Hitachi Cl ⁻ ISE			
Electrode 1 (K4269)	127	146	105
Electrode 2 ^c	113	108	105
Coulometric titration	—	109	107
Ektachem thin-film ISE	—	110	107

^a Plasma #1 and plasma #2 were sampled 8 days apart.

^b Measured by spectrophotometry after reaction with ferric ions.

^c Electrode lot number unknown.

close to the measured differences in recovery (14 and 38 mmol/L, respectively) between electrode #1 and electrode #2.

The fact that two Cl⁻ ISE cartridges responded differently to the same sample prompted us to investigate the possibility of variations among the cartridges, either on a lot-to-lot or cartridge-to-cartridge basis. Three different lots (K42, K27, and H90), two cartridges per lot, were tested with the same interfering ions used to test cartridge K4269 above. Only one of the cartridges tested (K2702) displayed fraction of unity values close to that previously reported by Boehringer Mannheim (14). The other five cartridges displayed widely varying fractions of unity for thiocyanate ion (between 8.38 and 22.24). These findings demonstrate that the interference selectivity varies from cartridge-to-cartridge, even within the same lot of membrane.

It has been reported that interference on the Beckman Synchron CX3 Cl⁻ ISE by bromide ions was

due to the cumulative effect of bromide ions on the Cl⁻ electrode (3). To determine whether the variable interference of Cl⁻ measurements by thiocyanate using a BM/Hitachi chemistry analyzer results from the cumulative effect of the interfering anion on the electrode membrane, potassium thiocyanate was spiked into a plasma pool to yield a final concentration of 2 mmol/L. The response of a Cl⁻ cartridge (H9086) to repeated exposure of the SCN⁻-spiked plasma is shown in Figure 3. No cumulative effect on this Cl⁻ cartridge was observed. Nor was there a carry over effect. The mean chloride value for the 88 SCN⁻-spiked plasma sample replicates was 128 mmol/L with a standard deviation of 1.9 mmol/L. The chloride values for the SCN⁻-free plasma pool varied between 101 and 102 mmol/L.

The variation in interference from cartridge-to-cartridge was also not due to deterioration in the electrode membrane because new cartridges with slopes around -53 mV had similar fractions of unity as older cartridges (K4269) with lower slopes (-42 mV).

The reagents for electrolyte measurements on the BM/Hitachi chemistry analyzers were prepared in house. To exclude the possibility that the increased fractions of unity for the interfering anions were due to the use of laboratory-prepared reagents, we compared the responses of two Cl⁻ cartridges (K4269 and O4015) to thiocyanate (0.5 to 5 mmol/L) using reagents obtained from the manufacturer or prepared in house. Cartridge O4015 was new at the time of this experiment. The fraction of unity for SCN⁻ ion with cartridge O4015 was 5.82 (using the manufacturer's reagent) and 4.98 (using the in-house reagent); the fraction of unity on cartridge K4269 was 18.02 and 18.93, respectively. Thus, no significant discrepancies were seen when using reagents from either source.

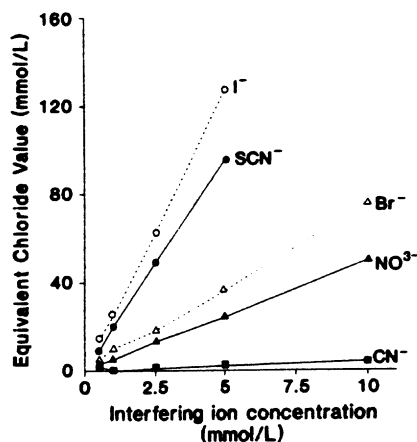


Figure 2 — Dose-response curves of a Hitachi Cl⁻ ion-selective electrode to different anions. Various amounts of sodium or potassium salts of the tested anions were spiked into a pooled plasma to yield final concentrations indicated in the X-axis. The plasmas were analyzed for Cl⁻ by a Hitachi Cl⁻ ISE (K4269). The Y-axis represents the chloride values contributed by the interfering ions obtained after subtracting the baseline chloride value.

Discussion

Chloride ISE has been widely used in clinical laboratories to assess the electrolyte status of a patient. However, erroneous Cl⁻ values have occasionally

TABLE 2
Hitachi Chloride Electrode Calibration Slopes and Sensitivity to Interfering Anions

	Electrode Lot Number							CMT ^a	BMC ^b
	K4269	K4237	K2702	K2782	H9089	H9086	Fraction of Unity		
Calibration slope (mV)	-42.2	-52.9	-49.7	-53.4	-51.6	-53.0			
Anions									
I ⁻	25.29	31.23	4.77	22.67	16.23	22.67	0.99	3.33	
SCN ⁻	18.93	22.24	1.80	17.72	8.38	12.96	1.26	2.00	
NO ₃ ⁻	4.92	5.21	1.62	4.25	3.79	3.49	—	1.11	
Br ⁻	3.77	4.29	1.73	3.64	2.83	2.90	0.89	1.43	
CN ⁻	0.13	0.07	0.11	0.19	0.14	0.07	0.02	—	
HCO ₃ ⁻	0.08	0.06	0.20	0.12	0.12	0.05	—	0.20	
F ⁻	-0.13	-0.06	—	—	—	—	—	0.26	
S ₂ O ₃ ²⁻	-0.10	-0.09	—	—	—	—	1.26	—	
SO ₄ ²⁻	-0.23	-0.11	—	—	—	—	—	0.27	

Fraction of unity is the slope of the regression line from a dose-response study and is expressed as mmol/L of chloride value contributed by each mmol/L of interfering ion.

^a Coulometric titration.

^b Boehringer Mannheim study (14).

been seen. For example, patients taking iodine supplementation, bromide-containing drugs, or sodium nitroprusside may have falsely elevated plasma Cl⁻ levels. On the other hand, patients with low bicarbonate levels may have slightly lower plasma Cl⁻ values, especially when the Cl⁻ is measured with a Hitachi Cl⁻ ISE (9,10). The mechanism and extent of interference of Cl⁻ measurements by certain anions depends on the type of Cl⁻ electrode employed.

Currently, there are two major types of Cl⁻ ISE used in the clinical laboratories: solid state Ag/AgCl electrodes and liquid/liquid ion-exchange membrane electrodes. The interference of anions on Ag/AgCl electrode is due to precipitation of the interfering

ion onto the electrode surface. For example, I⁻ can transform an Ag/AgCl electrode to an Ag/AgCl/AgI electrode that shows selectivity toward both Cl⁻ and I⁻. This effect is cumulative, as seen in the Beckman Synchron CX3 system (3), and can be corrected by polishing the electrode surface. The mechanism of interference of anions to chloride electrodes using liquid/liquid ion-exchangers with quaternary ammonium salts (e.g., the Hitachi Cl⁻ ISE) is not clear. It could be due to the strong interaction between interfering anions (e.g., SCN⁻) and quaternary ammonium salts (15,16). Therefore, it is possible that the interfering anions could enter the Cl⁻ ISE membrane, becoming a secondary counterion for quaternary ammonium (the primary counterion is Cl⁻). Because the anion-quaternary ammonium complex is mobile within the membrane, the secondary counterion may even reach a new equilibrium with the internal filling solution of the electrode (17). This process may be time dependent, that is, the sensitivity of Cl⁻ ISE toward interfering ions would increase with repeated exposure or due to aging as observed by Lipke *et al.* (10). However, our study did not support this hypothesis for the Hitachi Cl⁻ ISE because: repeated exposure of a Cl⁻ ISE cartridge to high concentrations of SCN⁻ did not change the response of this cartridge; two cartridges from the same lot (K4269 and K4237) with different on-line usage time (15 days and brand-new, respectively) showed similar results; two cartridges from the same lot (K2702 and K2782) with similar usage time (less than 3 days) had very different responses; and the same electrode (K4269) had the same response to SCN⁻ during a 9-day interval.

It has been suggested that the selectivity of the chloride electrode may depend on the chemical composition of the electrode membrane [e.g., dielectric constant of the solvent in liquid membrane (17)] or even on the physical property of the membrane (e.g.,

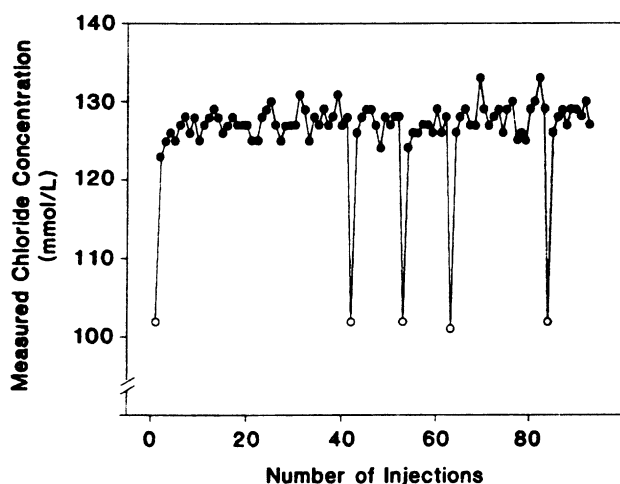


Figure 3 — Response of a Hitachi Cl⁻ ion-selective electrode (H9086) to repeated exposure of a pooled plasma spiked with 2 mmol/L potassium thiocyanate (closed circle). The same plasma pool without potassium thiocyanate (open circle) was also analyzed intermittently throughout this study. The control plasma had a Cl⁻ value of 102 mmol/L obtained by coulometric titration.

thickness). In manufacturing Cl^- ISE cartridges, 100 cartridges are made from a single membrane preparation. Heterogeneity of the membrane preparation (e.g., chemical composition and thickness) may contribute to the variation among these cartridges in terms of selectivity. Our study using reagents from different sources further suggests that the selectivity of the BM/Hitachi Cl^- electrode is the property of the electrode itself and is not influenced by the reagents.

It should be noted that even though different Hitachi Cl^- electrodes respond differently to interfering ions, they all yielded the same result for samples free of interfering ions. This may be due partially to the fact that the electrode is frequently calibrated to compensate for possible drifts. In addition, according to some people, high interference ratios may not be a completely undesirable event (12) because it could alert clinicians to the possible presence of bromide, cyanide, or other toxicities. Clinical biochemists should be aware of the possibility of erroneous Cl^- values, which usually express themselves as unusual anion gaps, and be able to confirm the presence of interference substances by independent methods.

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