The Role of Alkalinisation Therapy in Tricyclic Antidepressant Toxicity

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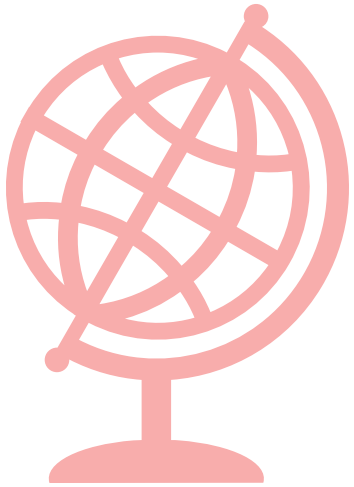
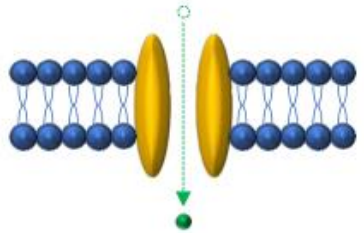
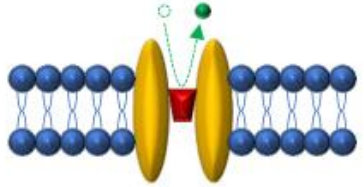
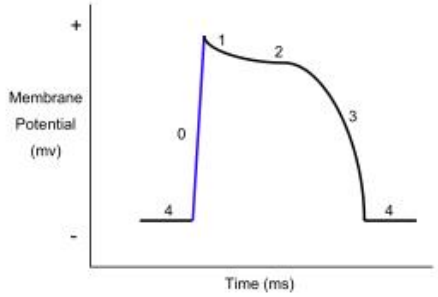
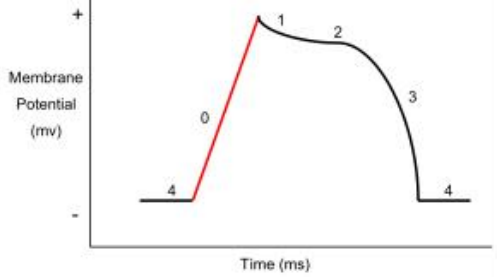
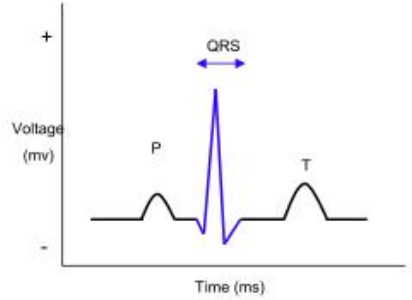
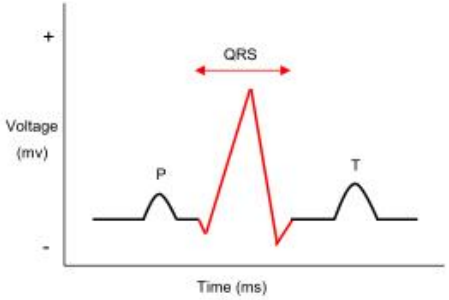
Epidemiology

Tricyclic Antidepressant (TCA) poisonings

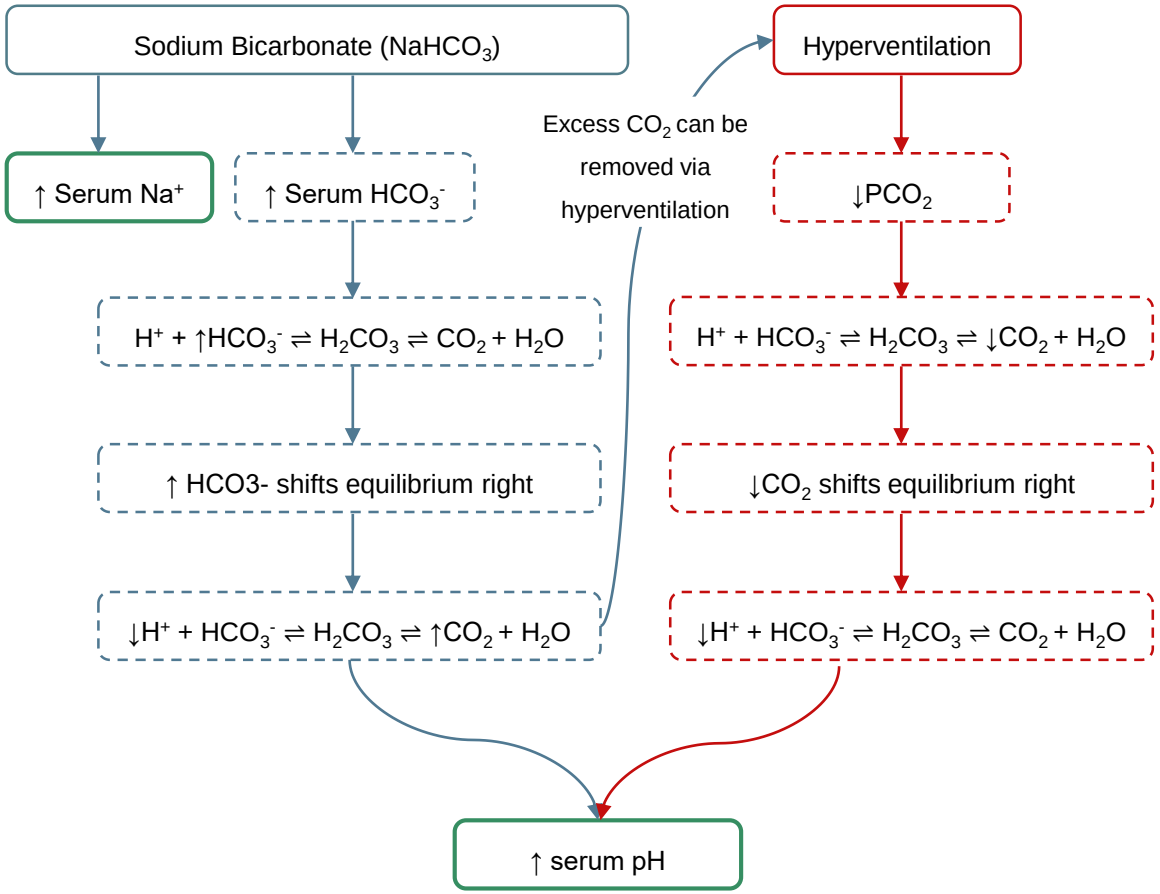
- TCAs have a relatively high toxicity profile
- No longer first-line treatment for depression
- Remain indicated in resistant depression
- During 2017 in the USA alone:
  - ~10,000 recorded cases
  - 73 reported fatalities
  - 2.2% of all poisoning-related mortalities



Pathophysiology

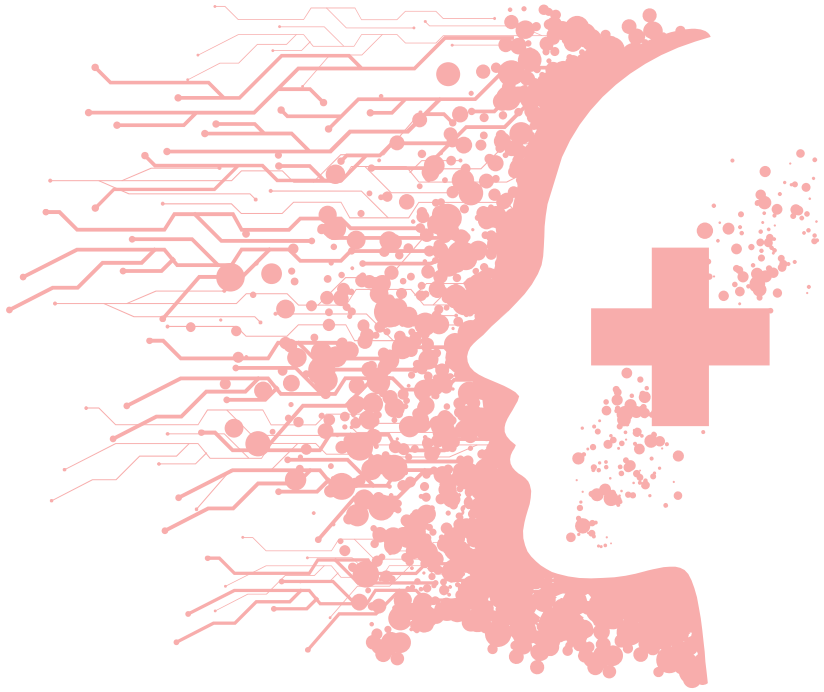
	Normal patient	TCA toxicity
Cardiac sodium channel		
Cardiac Action Potential		
ECG		
Legend	● = Sodium ion (Na^+) ▼ = free TCA	

Treatment


Sodium Bicarbonate ($NaHCO_3$)
Hyperventilation
Excess CO_2 can be removed via hyperventilation
↑ Serum Na^+
↑ Serum HCO_3^-
↓PCO_2
$H^+ + \uparrow HCO_3^- \rightleftharpoons H_2CO_3 \rightleftharpoons CO_2 + H_2O$
$H^+ + HCO_3^- \rightleftharpoons H_2CO_3 \rightleftharpoons \downarrow CO_2 + H_2O$
↑ HCO3- shifts equilibrium right
↓CO_2 shifts equilibrium right
$\downarrow H^+ + HCO_3^- \rightleftharpoons H_2CO_3 \rightleftharpoons \uparrow CO_2 + H_2O$
$\downarrow H^+ + HCO_3^- \rightleftharpoons H_2CO_3 \rightleftharpoons CO_2 + H_2O$
↑ serum pH

Gaps in the Literature

- Few studies support the need for therapeutic hyperventilation
- No study has quantified the effects of $NaHCO_3$ and hyperventilation on the biochemical profile
- Little evidence demonstrating therapeutic effects of $NaHCO_3$ and/or hyperventilation in humans
- Lack of guidelines for dosing $NaHCO_3$ and regulating hyperventilation



Objectives

To quantify the effects of $NaHCO_3$ and hyperventilation on:

- The biochemical profile (serum pH, $[Na^+]$)
- ECG findings (QRS interval)

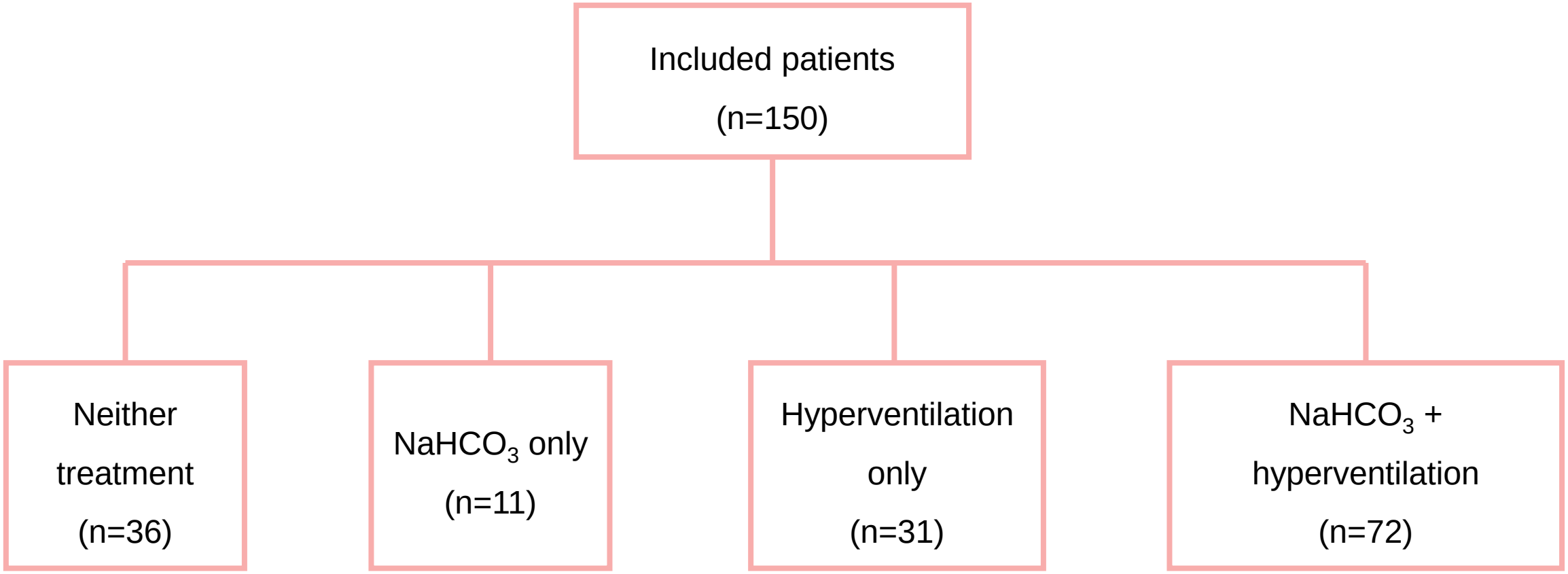
To test how accurately our mathematical model can predict increases in serum pH

To use our model to develop a nomogram for the dosage of $NaHCO_3$ and regulation of hyperventilation

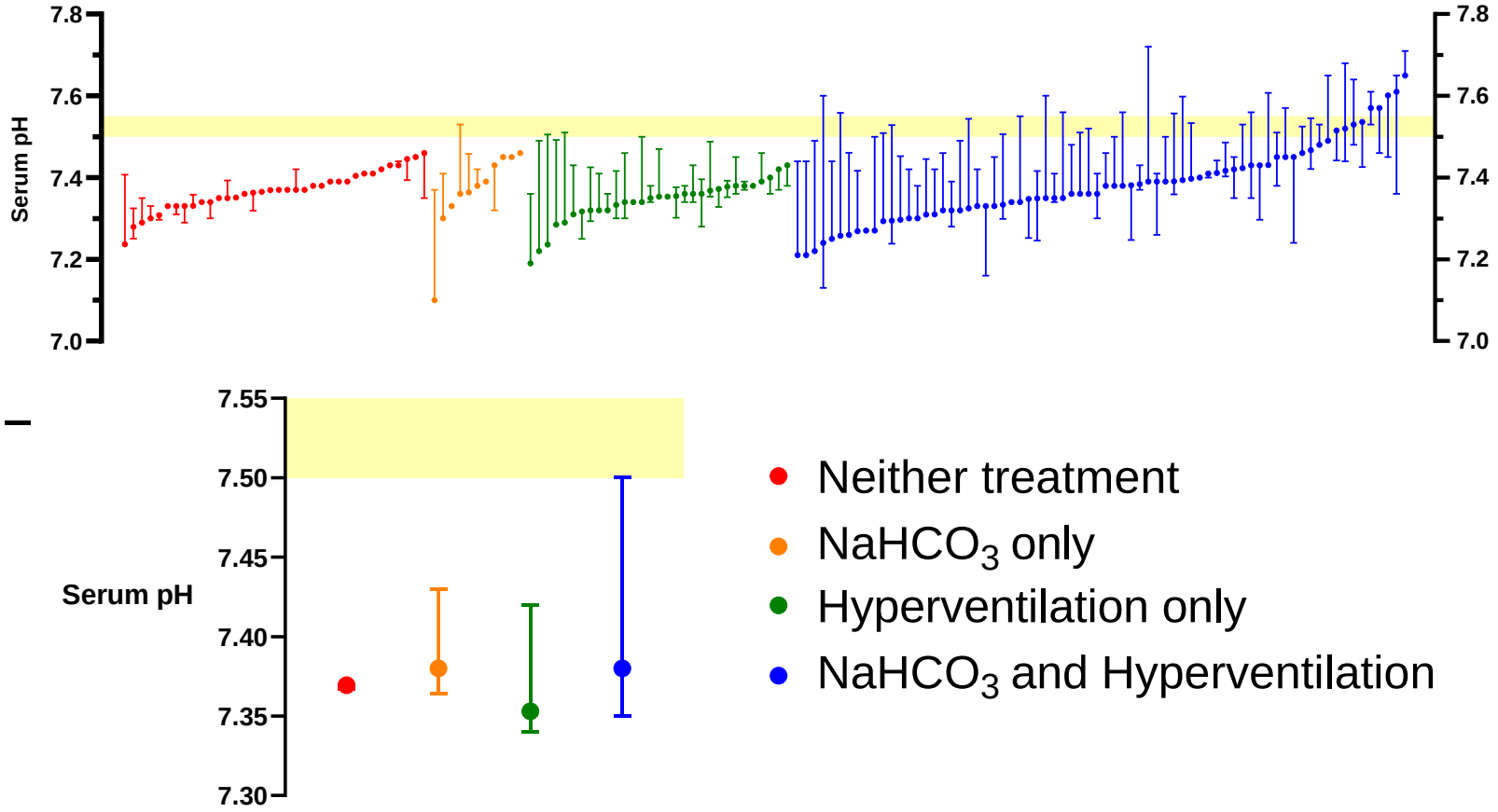
Methods

- 7 year retrospective review
- Patients ≥15yo with ≥10mg/kg TCA overdose
- Nation-wide
  - South Eastern Area Toxicology Service (SEATS)
  - Princess Alexandra Toxicology Service (PATS)
  - NSW Poisons Information Centre (PIC)
- Recorded serial blood gases and ECG
- Widened QRS is >110msec. Therapeutic narrowing of QRS if decrease by >30msec or to <100msec

Overview of Results



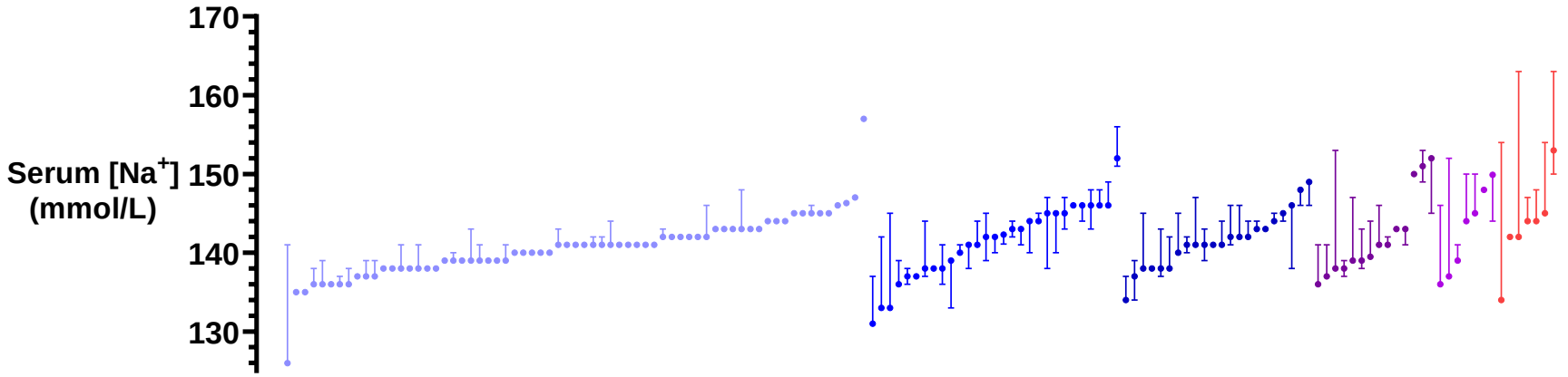
Serum Alkalinisation

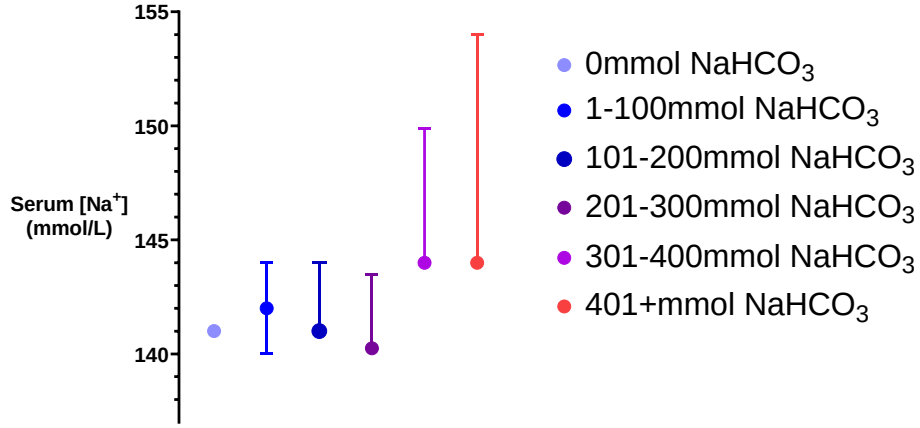


$NaHCO_3$ and hyperventilation worked best

…but further guidelines are required

Loading Serum Sodium with $NaHCO_3$



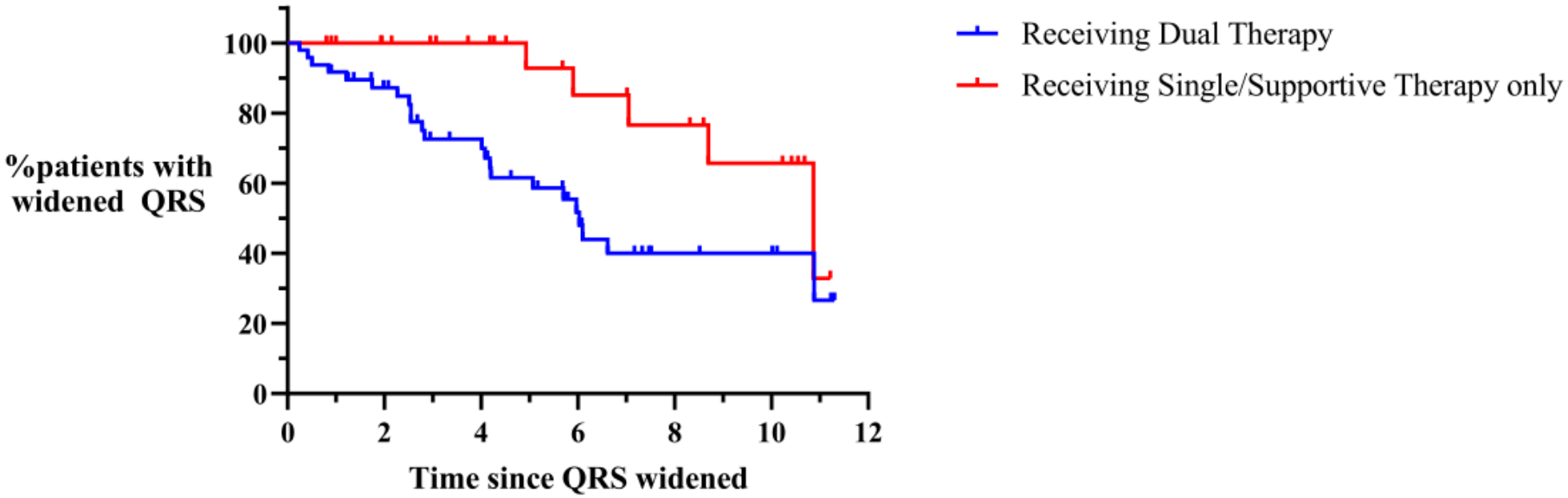


100-400mmol of $NaHCO_3$ seems appropriate for sodium loading

…but doses above 400mmol may risk hypernatremia

$NaHCO_3$ and hyperventilation and QRS narrowing

- QRS narrowing occurred **3x sooner** in the **dual therapy** group (n=51) compared to the **single/supportive therapy** group (n=33)
  - Cox regression: OR: 3.2, 95%CI: 1.2-8.2, p=0.02



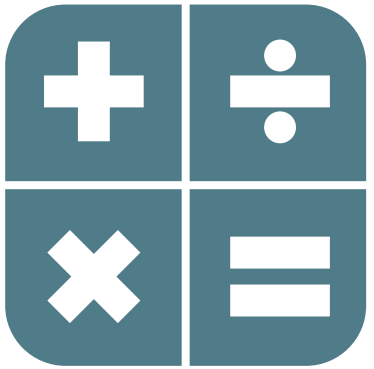
Predicting increases in pH following treatment

Predicting Serum pH:

$$[serum\ HCO_3^-]_{after\ Tx} = [serum\ HCO_3^-]_{before\ Tx} + \frac{NaHCO_3}{40} + 0.2 \times \Delta PCO_2$$

Using the Henderson-Hasselbalch equation:

$$pH_{after\ Tx} = 6.1 + \log\left(\frac{[serum\ HCO_3^-]_{after\ Tx}}{0.03 \times PCO_{2\ after\ Tx}}\right)$$



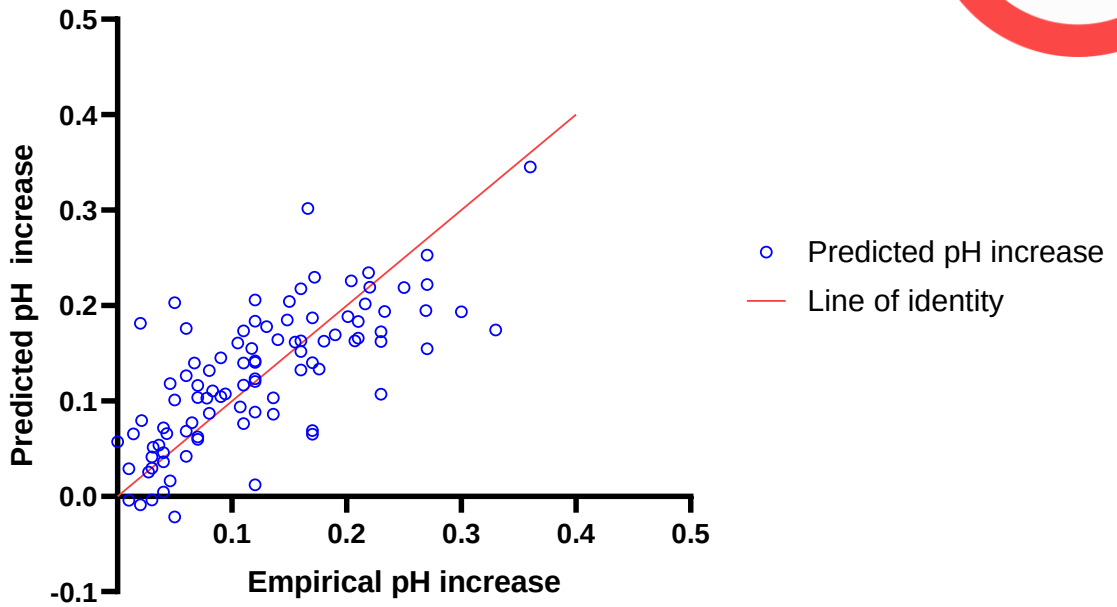
Accuracy of Equation

Intraclass correlation coefficient (ICC) - a measure of accuracy

0 = no accuracy, 1 = perfect accuracy

Serum pH:

ICC = 0.84 (95%CI: 0.77-0.90)



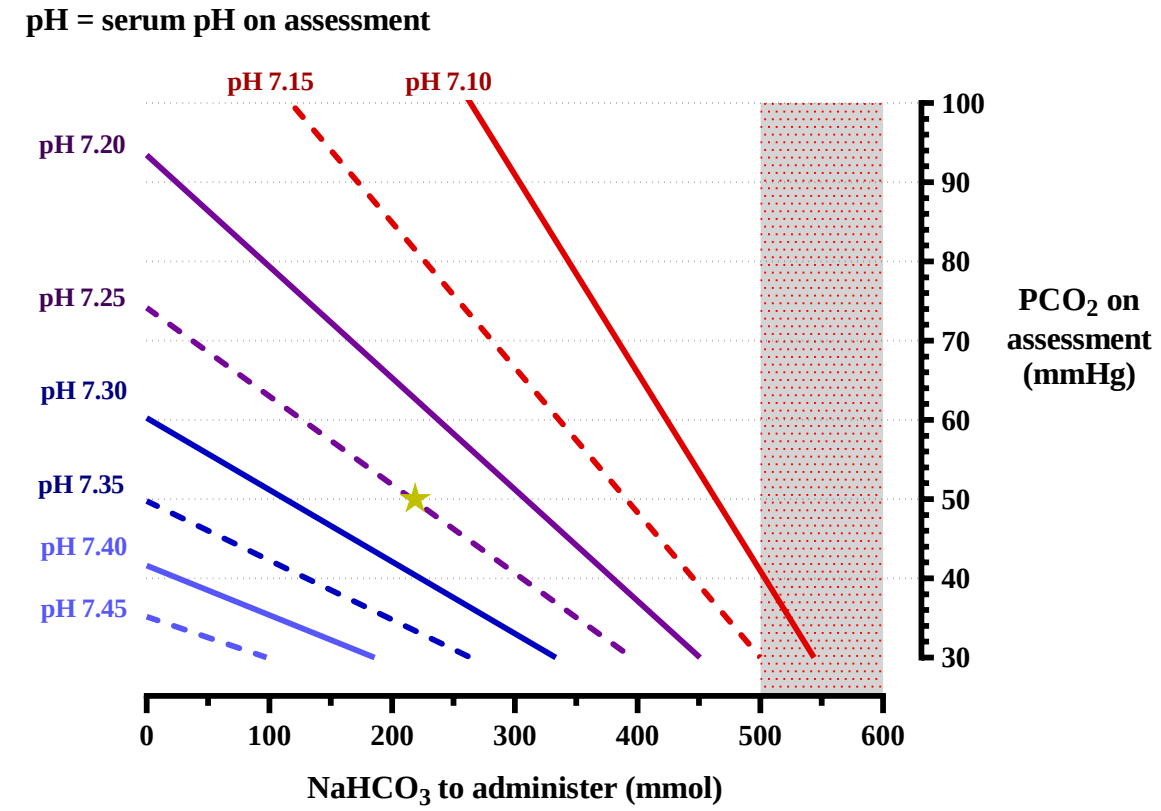
A nomogram for dosing $NaHCO_3$

Patient example:

- PCO_2 50mmHg
- Serum pH 7.25
- Recommended $NaHCO_3$ dose: 200-250mmol

The nomogram:

- Aims to increase pH to 7.50
- Assumes hyperventilation to PCO_2 30mmHg
- Caution with $NaHCO_3$ ≥500mmol



Conclusion

- Alkalinisation therapy is best achieved through **both $NaHCO_3$ and hyperventilation**
- These therapies can help **narrow QRS**
- We recommend hyperventilating patients to **PCO_2 30mmHg** and dosing $NaHCO_3$ according to our **nomogram**
- Caution should be applied with doses of $NaHCO_3$ beyond **400mmol**
- Therapy should be ceased if serum pH **>7.55** or if serum $[Na^+]$ increases by **>10mmol/L**

Questions?

Limitations and future directions

Limitations

Retrospective study:
- Incomplete or erroneous documentation
- Confounding treatments
- Non-uniform methods of measurement

Limited findings:
- Could not demonstrate therapeutic effects of treatments apart from QRS narrowing

Future directions

Prospective study (SODA 2):
- Uniform approach to treatment and observation
- Can assess benefits of treatment guidelines

Larger study:
- Investigate how other ECG markers (e.g. avR or R/S ratio) or clinical signs (e.g. hypotension) are affected by these treatments
- More standardised measurements (before AND after treatment)

Overview of Results

	$NaHCO_3$ group (IQR) n=86	No $NaHCO_3$ group (IQR) n=74	P-value
Dose of $NaHCO_3$	200 (100-300)	0	
Age	44 (28-57)	43 (27-51)	ns
Female	51 (59%)	52 (70%)	ns
Dose (g)	1.5 (1.3-2.5)	1.3 (1.0-1.8)	0.0010
Maximum HR (bpm)	124 (102-133)	105 (96-120)	0.0006
Minimum MAP (mmHg)	72 (65-84)	77 (70-89)	0.0159
Minimum GCS	3 (3-8)	10 (3-13)	<0.0001
Intubated	74 (86%)	32 (43%)	<0.0001
Maximum QRS (msec)	122 (108-138)	105 (94-115)	<0.0001
Length of stay	2.0 (1.3-2.7)	1.0 (0.6-1.8)	<0.0001
Seizure	11 (13%)	3 (4%)	ns
Death	1 (1%)	0	ns

Rules of thumb

Every 10mmHg decrease in PCO_2 increases serum pH by approximately 0.05

Every 100mmol of $NaHCO_3$ increases pH by approximately 0.05

ICC: 0.80 (95%CI: 0.71-0.87)

- Clinically simple to remember and implement
- Does not require nomogram's conditions

- Less accurate than Henderson-Hasselbalch equation
- pH change varies with patient biochemistry (HCO_3^- and PCO_2)

Mathematics behind nomogram

Assume final pH = 7.50, final PCO_2=30mmHg. Sub into H-H equation	$7.5 = 6.1 + \log\left(\frac{[serum\ HCO_3^-]_{after\ Tx}}{0.03 \times 30}\right)$ ➔ $[Serum\ HCO_3^-]_{after\ Tx} = 22.6mmol/L$
From our equations:	$[serum\ HCO_3^-]_{after\ Tx} = [serum\ HCO_3^-]_{before\ Tx} + \frac{NaHCO_3}{40} + 0.2 \times \Delta PCO2$
Rearranging Henderson-Hasselbalch equation:	$[serum\ HCO_3^-]_{before\ Tx} = 10^{pH_{before\ Tx} - 6.1} \times 0.03 \times PCO_{2\ before\ Tx}$
Y-axis is PCO_2 on assessment and x-axis is recommended dose of $NaHCO_3$. Substituting previous:	$22.6 = 10^{pH_{before\ Tx} - 6.1} \times 0.03 \times y + \frac{x}{40} + 0.2(30 - y)$
Rearrange for y:	$y = \frac{x - 664}{8 - 1.2 \times 10^{pH_{before\ Tx} - 6.1}}$
Substitute pH (e.g. 7.25)	$y = \frac{x - 664}{-9.0}$

Bland-Altman Analysis