

Fig. 2 and Fig. 3 are algorithms for the consideration of primary and mixed acid–base disorders.⁴

Limitations of blood gas analysis

The blood gas analysis cannot yield a specific diagnosis. A patient with asthma may have similar values to another patient with pneumonia. Alternatively, a patient with chronic obstructive pulmonary disease and respiratory failure may have similar results to a patient with pulmonary oedema.

The analysis does not reflect the degree to which an abnormality actually affects a patient. A low PaO₂ does not necessarily indicate tissue hypoxia, nor does a normal PaO₂ indicate adequate tissue oxygenation. Oxygen utilisation is influenced by other factors such as regional blood flow, haemoglobin affinity for oxygen and cardiac output.

Blood gas analysis cannot be used as a screening test for early pulmonary disease. Severe disease may be present before significant changes are seen in blood gases.

Venous blood gases

It is easier to obtain a venous sample than an arterial sample. In some situations analysis of venous blood can provide enough information to assist in clinical decisions. In general, the pH, CO₂ and HCO₃⁻ values are similar in venous and arterial blood (Box 1). The main difference is the partial pressure of oxygen in venous blood is less than half that of arterial blood. Venous blood should not therefore be used to assess oxygenation.

Conclusion

Measuring arterial blood gases can be a useful adjunct to the assessment of patients with either acute or chronic diseases. The results show if the patient is acidaemic or alkalaemic and whether the cause is likely to have a respiratory or metabolic

component. The PaCO₂ reflects alveolar ventilation and the PaO₂ reflects the oxygenation of arterial blood. When combined with a patient's clinical features, blood gas analysis can facilitate diagnosis and management.

References

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2. Harsten A, Berg B, Inerot S, Muth L. Importance of correct handling of samples for the results of blood gas analysis. *Acta Anaesthesiol Scand* 1988;32:365-8.
3. Williams AJ. ABC of oxygen: assessing and interpreting arterial blood gases and acid-base balance. *BMJ* 1998;317:1213-6.
4. Drage S, Wilkinson D. Acid base balance. Update 13. 2001. World Federation of Societies of Anaesthesiologists. <http://update.anaesthesiologists.org/wp-content/uploads/2009/09/Acid-Base-Balance-Update-13.pdf> [cited 2010 Jul 7]

Further reading

Martin L. All you really need to know to interpret arterial blood gases. 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 1999.

Conflict of interest: none declared

Self-test questions

The following statements are either true or false (answers on page 131)

7. The partial pressure of carbon dioxide in arterial blood (PaCO₂) is inversely related to alveolar ventilation.
8. The partial pressure of oxygen in arterial blood (PaO₂) reflects the gas exchange function of the lungs.

New drugs

Some of the views expressed in the following notes on newly approved products should be regarded as tentative, as there may be limited published data and little experience in Australia of their safety or efficacy. However, the Editorial Executive Committee believes that comments made in good faith at an early stage may still be of value. As a result of fuller experience, initial comments may need to be modified. The Committee is prepared to do this. Before new drugs are prescribed, the Committee believes it is important that full information is obtained either from the manufacturer's approved product information, a drug information centre or some other appropriate source.

Certolizumab

Cimzia (UCB)

pre-filled syringe containing 200 mg in 1 mL of liquid

Approved indication: rheumatoid arthritis

Australian Medicines Handbook section 15.2.1

Certolizumab, like adalimumab, etanercept and infliximab, is a tumour necrosis factor inhibitor indicated for rheumatoid arthritis. It is a recombinant humanised antibody Fab' fragment

which has been pegylated to extend its plasma half-life to that of the whole antibody.

Peak plasma concentrations are reached between 54 and 171 hours after subcutaneous administration and its bioavailability is approximately 80%. The terminal elimination half-life is around 14 days. However, the presence of antibodies to certolizumab increases its clearance and appears to correlate with reduced patient responses. Giving methotrexate concomitantly with certolizumab reduces the formation of anti-certolizumab antibodies.

Certolizumab is indicated for adults with moderate to severely active rheumatoid arthritis. It should be combined with methotrexate in patients who have had an inadequate response to or are intolerant to other treatments with one or more disease-modifying antirheumatic drugs. Certolizumab should only be given on its own if methotrexate is contraindicated or not tolerated.

The efficacy of certolizumab has been studied in three placebo-controlled phase III trials. One of the studies was in 982 patients with active rheumatoid arthritis who had not responded to methotrexate therapy alone. Fortnightly certolizumab (three initial 400 mg doses followed by a maintenance dose of 200 mg or 400 mg given subcutaneously) or placebo was added to methotrexate treatment. (For this trial, certolizumab was reconstituted from lyophilised powder.) Patients' response to therapy was measured over 52 weeks according to the American College of Rheumatology 20% (ACR20) criteria for improvement. This is a composite outcome based on the number of swollen and tender joints, the erythrocyte sedimentation rate or C-reactive protein concentration and global assessments of arthritis activity by the patient and doctor. Joint damage was also assessed by radiology using a modified Sharp score.¹

Certolizumab significantly reduced the signs and symptoms of rheumatoid arthritis compared to placebo. After 24 weeks, 58.8% and 60.8% of patients receiving 200 mg and 400 mg of certolizumab had an ACR20 response compared to 13.6% in the placebo group. Progression of joint damage was significantly less with certolizumab than with placebo – at week 52, mean changes in the Sharp score from baseline were 0.4 units for certolizumab 200 mg, 0.2 units for certolizumab 400 mg and 2.8 units with placebo. The higher certolizumab dose did not seem to offer any additional clinical benefit over the lower dose.¹

In the trial, adverse events were comparable between groups with headache, hypertension and back pain being the most common non-infectious events. However, headache was more common with placebo (12% of patients) and hypertension was more common with certolizumab (9.2% of patients). Seven patients died while receiving treatment – one in the placebo group (cardiac arrest) and six in the certolizumab groups (hepatic neoplasm and cardiac arrest with 200 mg dose and stroke, cardiac arrest, atrial fibrillation and fatigue, and myocardial necrosis with 400 mg dose). Twelve patients receiving certolizumab withdrew because of infection. There were no withdrawals due to infection in the placebo group. Serious infections included lower respiratory tract infections, gastroenteritis, urinary tract infections and tuberculosis. Malignancies were found in 12 patients – 1/199 receiving placebo and 11/781 receiving certolizumab. At week 52, 6.4% of patients receiving certolizumab had antibodies to the study drug.¹

Another phase III trial (619 patients) with a similar design, but using liquid certolizumab, showed similar rates of efficacy

in rheumatoid arthritis after 24 weeks of treatment (ACR20 rates: 57–58% with certolizumab vs 9% with placebo). Serious infections occurred with certolizumab but not with placebo (3.2% and 2.4% of patients receiving certolizumab 200 mg and 400 mg vs 0% receiving placebo). Infections included tuberculosis, gastroenteritis, skin infections, postoperative wound infection, tooth abscess, urosepsis, pneumonia, upper respiratory tract infection and sinusitis. There was one case of lupus erythematosus rash with certolizumab 200 mg.²

Certolizumab without methotrexate has been assessed in a trial of 220 patients who received either certolizumab 400 mg or placebo every four weeks. After 24 weeks, 45.5% of patients receiving monotherapy had responded (ACR20) compared to only 9.3% of patients receiving placebo. Adverse effects were seen in 75.6% (84 of 111) of the people in the certolizumab group versus 57.8% (63 of 109) in the placebo group. These were mostly mild or moderate but there were three serious events with placebo (vomiting, chronic renal failure, pneumonitis) and eight with certolizumab (aggravated rheumatoid arthritis (two cases), bacterial arthritis, mastitis, benign parathyroid tumour, postural dizziness, ischaemic stroke and uterine bleeding).³

An open-label extension study in 402 patients indicated that the benefits of certolizumab (with or without methotrexate) may not be sustained over prolonged periods (up to 112 weeks) in some people. The presence of anti-certolizumab antibodies seemed to reduce the likelihood of maintaining a response to treatment.

As certolizumab modulates the immune system there is a risk of serious infection. It is contraindicated in active tuberculosis and other serious infections such as sepsis or opportunistic infections. Patients should be tested for active or latent tuberculosis before and during treatment. Reactivation of hepatitis B virus has been reported with certolizumab so carriers should be closely monitored for active infection. Once treatment is stopped, elimination of certolizumab may take five months, so monitoring should be continued for this period. Caution is also urged when considering certolizumab for patients with a history of cancer or demyelinating disorders.

This drug is contraindicated in patients with moderate to severe congestive heart failure. It should not be used in combination with anakinra or abatacept. Live or attenuated vaccines should not be given with certolizumab and it should not be used in pregnancy.

Certolizumab offers an alternative to patients who have not responded to other rheumatoid arthritis treatments. About two-thirds of patients in the trials responded to certolizumab when it was added to methotrexate.^{1,2} Certolizumab also showed some efficacy when given as a monotherapy although response rates were 10–20% lower without methotrexate. It is not known how certolizumab will compare to the other tumour necrosis factor inhibitors as there have been no comparative trials so far.

T T manufacturer provided additional useful information

References ^{†A}

1. Keystone E, van der Heijde D, Mason D Jr, Landewé R, van Vollenhoven R, Combe B, et al. Certolizumab pegol plus methotrexate is significantly more effective than placebo plus methotrexate in active rheumatoid arthritis: findings of a fifty-two-week, phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group study. *Arthritis Rheum* 2008;58:3319-29.
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3. Fleischmann R, Vencovsky J, van Vollenhoven RF, Boronstein D, Box J, Coteur G, et al. Efficacy and safety of certolizumab pegol monotherapy every 4 weeks in patients with rheumatoid arthritis failing previous disease-modifying antirheumatic therapy: the FAST4WARD study. *Ann Rheum Dis* 2009;68:805-11.

The T-score (**T**) is explained in 'New drugs: transparency', *Aust Prescr* 2009;32:80-1.

[†] At the time the comment was prepared, a scientific discussion about this drug was available on the website of the European Medicines Agency (www.ema.europa.eu).

^A At the time the comment was prepared, information about this drug was available on the website of the Therapeutic Goods Administration (www.tga.gov.au/pmeds/auspar.htm)

Corrections

New drugs: Nebivolol (*Aust Prescr* 2010;33:55-6)

Following receipt of correspondence, which is published on pages 101-2 in this issue, the New drug comment on nebivolol has been corrected as follows.

In paragraph 6 the third sentence has been deleted ('This was a *post hoc* analysis ... different doses of nebivolol.')

Also in paragraph 6, the fifth sentence ('The target dose ... compared to placebo.') has been corrected to 'The target dose was reached by two-thirds of the patients in the nebivolol group. Nebivolol was associated with a significant reduction (absolute risk reduction of 4.2%) in the composite end point of all-cause mortality or hospitalisation (due to a cardiovascular event), compared to placebo.'

Reference 5 has been replaced by

5. Flather MD, Shibata MC, Coats AJ, Van Veldhuisen DJ, Parkhomenko A, Borbola J, et al.; SENIORS Investigators. Randomized trial to determine the effect of nebivolol on mortality and cardiovascular hospital admission in elderly patients with heart failure (SENIORS). *Eur Heart J* 2005;26:215-25.

New drugs: Miglustat (*Aust Prescr* 2010;33:92-3)

Paragraph 4 should start 'Regular intravenous infusion of recombinant glucocerebrosidase ...'.

Self-test questions (*Aust Prescr* 2010;33:84-7)

Questions 1 and 2 on page 87 should be 3 and 4.

Answers to self-test questions

- | | | | |
|----------|----------|---------|---------|
| 1. False | 3. False | 5. True | 7. True |
| 2. False | 4. False | 6. True | 8. True |

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For general correspondence such as Letters to the Editor, contact the Editor.

Telephone: (02) 6202 3100 Fax: (02) 6282 6855

Postal: The Editor
Australian Prescriber
Suite 3, 2 Phipps Close
DEAKIN ACT 2600

Email: info@australianprescriber.com

Website: www.australianprescriber.com