Findings that shed new light on the possible pathogenesis of a disease or an adverse effect

Complete AV-block secondary to lithium-clozapine therapy and relapsing multiple sclerosis in a bipolar patient

Edward EE Gabeler, Addy JM van Miltenburg

Cardiology Department, Sint Franciscus Gasthuis, Rotterdam, Netherlands

Correspondence to Dr Edward EE Gabeler, eegabeler@hotmail.com

Summary

A complete atrioventricular block (CAVB) can be a lethal complication when it is not treated directly with isoprenaline and pacemaker therapy. The overall incidence of CAVB varies between 4 to 8 per cent with a mortality OR of 3.2 within 30 days if untreated. Main causes of CAVB are inferior myocardial infarction, congenital AV node malformation, mitral valve insufficiency and valve surgery, metabolic disorders and intoxications. The authors describe a case with a CAVB due to lithium-clozapine therapy and relapsing multiple sclerosis.

BACKGROUND

According to the American Heart Association/American College of Cardiology guidelines, complete atrioventricular block (CAVB) is a class I level C indication for internal pacemaker therapy due to the risk of ventricular fibrillation and sudden cardiac death.¹ We describe a case of CAVB in a patient with bipolar affective disorder due to 11 years of lithium-clozapine therapy and relapsing multiple sclerosis (MS) since 1996. The bipolar disorder was earlier diagnosed by postpartum depression and psychotic episodes. Therefore, high dosages of 600 mg lithium and 525 mg clozapine per day were taken.

CASE PRESENTATION

A 53-year-old woman was admitted to our coronary care unit, suffering from progressive dizziness, palpitations and collapses since a week. Since June 2009, postural orthostatic hypotension (POTS) was present. This was retrospectively a side effect of lithium and clozapine. She never had heart complaints. Forlax and loperamide were occasionally taken for irritable bowel syndrome.

INVESTIGATIONS

On examination, she was obese (length: 1.68 m, weight 98 kgs, body mass index 35) with bradyfrenia, had Adam-Stokes attacks and a blood pressure (BP) of 160/90 mm Hg at a pulse of 22 beats per min (bpm). The central venous pressure was increased, and the heart sounds were soft. No murmurs were heard. Besides bilateral ankle oedema, neither pulmonary, nor abdominal abnormalities were found. Neurological evaluation showed preexistent bilateral sacular eyemovements, decreased dexterity and hypesthesia of her right hand and legs with bilateral Babinsky reflexes. Her electrocardiogram (EKG) showed AV-dissociation with CAVB and ventricular escape rhythm of 22 bpm (figure 1a). Her serum lithium concentration was normal (0.7 mmol/l). Clozapine was not measured. Her thyroid function, blood chemistry and haematology were normal. Rare infectious

causes of CAVB, like *Borrelia Burgdorfferi* and *Salmonella typhi*, were anamnesticly not likely. The chest x-ray and echocardiography were normal. A brain MRI showed pre-existent white matter lesions of the periventricular region and corpus callosum.

DIFFERENTIAL DIAGNOSIS

Complete AV block due to:

- ▶ Adverse effects of medication like lithium and clozapine
- ▶ Relapsing MS (Schubs)
- ▶ Myocardial ischemia
- ▶ Valvular insufficiency
- ▶ Hypothyroidism
- ▶ Metabolic disorders

TREATMENT

Intravenous isoprenaline increased the heart rate to 34 bpm and the BP to 170/95 mm Hg. A temporary external pacemakerlead was given for safeguarding. A permanent pacemaker dual chamber stimulation, dual chamber sensing, dual chamber tracking or inhibition, independent rate modulation (DDDR) was finally inserted.

OUTCOME AND FOLLOW-UP

After a temporary external pacemaker lead, an internal pacemaker (DDDR) was inserted which paced adequately (figure 1b). Lithium and clozapine were continued for treating her bipolar disorder, because of severe bipolar relapses if not given as earlier experienced. Thus, reversibility of CAVB could not be tested. She was discharged in good condition.

DISCUSSION

The CAVB in our case is hypothetically caused by cumulating effects of lithium, clozapine at normal serum levels and relapsing MS.

Figure 1 a) Atrioventricular dissociation with complete atrioventricular block and a ventricular escape rhythm of 22 bpm at a left axis and with QT elongation and an occasional capture beat. In leads I, II, aVR, aVL, aVF and V5 muscle interference is registered. b) pacemaker rhythm of 80 bpm.

First, lithium decreases the spontaneous depolarisation of the sinus node, and conduction velocity in AV and intraventricular conduction systems. Furthermore, the adrenergic response is reduced and the calcium influx during sinus pacing is modulated. The potential of lithium to induce sinus node disease, arrhythmia, myocarditis and Brugada-type-EKG-changes with an increased mortality is known.² Shikari *et al* indicated that lithium is a potential blocker of the AV node at any dosage.³ However, causing pacemaker dependent CAVB is a rarity within the therapeutic range.

Second, side effects of clozapine, an atypical neuroleptic noradrenalytic and parasympatholytic dibenzodiazepinderivative, are POTS, myocarditis, myopathy and QT elongation. Krobert *et al* described that clozapine in vitro desensitises the α -adrenoceptor,⁴ thus spontaneous sinus node depolarising may be hindered and adrenergic sensitivity decreased. Vaddadj *et al* reported that clozapine decreases selenium, an antioxidant of importance in myocarditis recovery, thus impairing the repair capacity of a damaged conductive system (CS).⁵ Third, relapsing MS

may damage the conductive system and may increase the basic vagal tone, inhibiting sinoatrial node (SN) and AV conduction. Drouin *et al* described QT elongation as a result of MS in patients and in an animal model.⁶ Summarising, the combined therapy of bipolar disorder and relapsing MS may cause a decreased depolarisation in SN, AV, bundle of His and CS, may cause an increased refractory period with QT elongation, may cause a reduced adrenergic response and a damaged CS with an impaired repair capacity, leading to CAVB. Therefore, we emphasise that regular screening for detection of conduction disorder is necessary.

Learning points

- ▶ Lithium and clozapine inhibit AV conductivity.
- ▶ Lithium-clozapine therapy with relapsing Schubs damage the AV conductive system.
- ▶ EKG screening is mandatory in bipolar patients with MS.

Competing interests None.

Patient consent Obtained.

REFERENCES

1. **Gregoratos G**. ACC/AHA guidelines for implantation of cardiac pacemakers and antiarrhythmia devices. *Circulation* 1998;**97**:1325–35.
2. **Talati SN**, Aslam AF, Vasavada B. Sinus node dysfunction in association with chronic lithium therapy: a case report and review of literature. *Am J Ther* 2009;**16**:274–8.
3. **Shiraki T**, Kohno K, Saito D, *et al*. Complete atrioventricular block secondary to lithium therapy. *Circ J* 2008;**72**:847–9.
4. **Krobert KA**, Andressen KW, Levy FO. Heterologous desensitization is evoked by both agonist and antagonist stimulation of the human 5-HT(7) serotonin receptor. *Eur J Pharmacol* 2006;**532**:1–10.
5. **Vaddadi KS**, Soosai E, Vaddadi G. Low blood selenium concentrations in schizophrenic patients on clozapine. *Br J Clin Pharmacol* 2003;**55**:307–9.
6. **Drouin E**, Nataf S, Lande G, *et al*. Abnormalities of cardiac repolarization in multiple sclerosis: relationship with a model of allergic encephalomyelitis in rat. *Muscle Nerve* 1998;**21**:940–2.

This pdf has been created automatically from the final edited text and images.

Copyright 2011 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit <http://group.bmj.com/group/rights-licensing/permissions>.

BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Please cite this article as follows (you will need to access the article online to obtain the date of publication).

Gabeler EEE, van Miltenburg AJM. Complete AV-block secondary to lithium-clozapine therapy and relapsing multiple sclerosis in a bipolar patient. *BMJ Case Reports* 2011;10.1136/bcr.10.2011.5030, Published XXX

Become a Fellow of BMJ Case Reports today and you can:

- Submit as many cases as you like
- Enjoy fast sympathetic peer review and rapid publication of accepted articles
- Access all the published articles
- Re-use any of the published material for personal use and teaching without further permission

For information on Institutional Fellowships contact consortiasales@bmjgroup.com

Visit casereports.bmj.com for more articles like this and to become a Fellow