

CASE REPORT

INTERMEDIATE

CLINICAL CASE

Probenecid

An Oral Inotrope for End-Stage Heart Failure in a Case With Myotonic Dystrophy



Evan C. Klein, MD,^a Jack Rubinstein, MD,^b Jennifer L. Strande, MD, PhD^{a,c}

ABSTRACT

A 56-year-old man with multiple cardiac manifestations of type 1 myotonic dystrophy, including severe, nonischemic cardiomyopathy, presented in refractory cardiogenic shock requiring inotropic therapy. Given his wishes to die without having any intravenous medications, he was started on oral probenecid therapy, which allowed for successful elimination of his intravenous therapies. (**Level of Difficulty: Intermediate.**) (J Am Coll Cardiol Case Rep 2019;1:213-7)
© 2019 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

HISTORY OF PRESENTING ILLNESS

A 56-year-old man presented for shortness of breath. He described several months of worsening dyspnea with orthopnea, bendopnea, paroxysmal nocturnal dyspnea, and a 7-pound weight gain. During this time, he limited physical activities to the point where

he was sleeping upright in his recliner and relying on assistance for activities of daily living.

Physical examination revealed a thin, cachectic man who appeared older than his stated age. He was tachycardic, with a biventricular paced rhythm, and hypoxic, with an oxygen saturation of 88%. He had a mechanical S₁ with a grade 1 out of 6 apical holosystolic murmur, an estimated jugular venous pressure >25 cm H₂O, bibasilar rales, and cool bilateral lower extremities, with 2+ pitting edema to the upper thighs.

LEARNING OBJECTIVES

- Although the cardiac complications of muscular dystrophy are variable and can affect both electrical conduction and mechanical myocardial function, advanced therapies in these patients can sometimes be limited by their muscular atrophy and severe deconditioning.
- Probenecid may be a viable oral beta-adrenergic independent adjunctive therapy, or it may replace standard intravenous inotropes in patients with end-stage cardiomyopathy.

PAST MEDICAL HISTORY

The patient's history was significant for advanced type 1 myotonic dystrophy complicated by muscle weakness and recurrent falls, paroxysmal atrial tachycardia, bileaflet mitral valve prolapse with severe posteriorly directed mitral valve regurgitation, and nonischemic cardiomyopathy. His calculated left ventricular ejection fraction improved from 35% to 60% as his mitral regurgitation progressively

From the ^aDivision of Cardiovascular Medicine, Medical College of Wisconsin, Milwaukee, Wisconsin; ^bDivision of Cardiovascular Medicine, University of Cincinnati, Cincinnati, Ohio; and the ^cDepartment of Cell Biology, Neurobiology, and Anatomy, Medical College of Wisconsin, Milwaukee, Wisconsin. Dr. Rubinstein is a founding member of CinTRYP, LLC; and has received royalties from this venture. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received April 12, 2019; revised manuscript received June 27, 2019, accepted July 7, 2019.

**ABBREVIATIONS
AND ACRONYMS****CTG** = cytosine-thymine-guanine**CUG** = cytosine-uracil-guanine**DM1** = type 1 myotonic dystrophy**INR** = international normalized ratio**LVEF** = left ventricular ejection fraction**NT-proBNP** = N-terminal pro B-type natriuretic peptide**NYHA** = New York Heart Association**RNA** = ribonucleic acid**SVC** = superior vena cava**TRPV-2** = transient receptor potential vanilloid-2 subtype

worsened over the 10 to 12 years before presentation, and this improvement was temporally unrelated to cardiac resynchronization therapy. Six months before presentation, he underwent mitral valve replacement with a 31-mm St. Jude mechanical valve (St. Jude, St. Paul, Minnesota). This procedure was complicated by mild paravalvular mitral regurgitation.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis included cardiogenic shock secondary to end-stage heart failure versus complications of mitral valve replacement or less likely secondary to acute coronary syndrome or thrombosis of his mechanical mitral valve.

INITIAL INVESTIGATIONS

Blood test results were as follows: N-terminal pro-B-type natriuretic peptide, 6,208 pg/ml (reference <125 pg/ml); international normalized ratio, 6.8; troponin I, 0.05 (reference, 0.00 to 0.10); and lactate, 1.4 mmol/l (reference 0.5 to 1.6 mmol/l). The electrocardiogram showed a biventricular paced rhythm. The chest radiograph showed cardiomegaly with mild pulmonary vascular congestion. Initial treatment with escalating doses of intravenous diuretic agents was met with oliguria, hypotension, tachycardia, altered mental status, and elevated lactate (3.5 mmol/l). A superior vena cava (SVC) oxygen saturation at this time measured 36%. A transthoracic echocardiogram revealed severe left ventricular systolic dysfunction with an estimated left ventricular ejection fraction of 20% and mild paravalvular mitral regurgitation.

MANAGEMENT

Intravenous dobutamine at 5 µg/kg/min improved his mental status, urine output, heart rate, lactate (1.3 mmol/l), and SVC oxygen saturation (61.5%), but because of paroxysms of atrial tachycardia, he required a transition to milrinone. During the 3- to 4-hour period between inotropes, the patient redeveloped altered mental status, hypotension, oliguria, rising lactate (2.3 mmol/l), and reduced SVC oxygen saturation (26%). Symptoms and urine output improved, lactic acidosis resolved, and SVC oxygen saturation increased to 63.5% shortly after he started on milrinone. At this point, right-sided heart catheterization during milrinone therapy at 0.375 µg/kg/min showed an assumed Fick cardiac output and cardiac

index of 4.53 and 2.33 and a pulmonary capillary wedge pressure of 15 mm Hg without v-waves suggestive of significant mitral regurgitation. Notably, his mixed venous saturation of 63.6% corresponded well to his SVC oxygen saturation of 63.5%.

Despite adequate diuresis, attempts to wean him from intravenous inotropes were met with lethargy, confusion, tachycardia, oliguria, and reduced SVC oxygen saturation. Given his poor prognosis, the patient's overall condition was discussed with his neurology consultants. It was determined that the patient should not be a candidate for advanced cardiac therapies because of his severe muscular atrophy and deconditioning, which would leave him unable to manage a ventricular assist device without 24-H assistive care. At this point, supportive (palliative) care was recommended, and goals of care were readdressed with the patient, who stated that he wished to go home without intravenous therapies to enjoy his new recliner and 60-inch television.

As an attempt to meet his goals, the patient was offered a trial of oral probenecid with the aim of weaning him from intravenous inotrope therapy. Probenecid is a relatively selective transient receptor potential vanilloid-2 subtype (TRPV-2) calcium-channel agonist that increases myocardial inotropy and lusitropy without increasing arrhythmic burden in murine models (1). Informed consent was obtained, given the off-label use. The patient was started on probenecid 1,000 mg by mouth twice daily while he was weaned from milrinone without recurrence of mental status, heart rate, or urine output changes and with improvement in serum creatinine levels. The protocol of drug titration and the resultant SVC oxygen saturations, estimated cardiac outputs, heart rates, urine outputs, serum creatinine, and serum lactate levels can be seen in [Table 1](#). A visual representation of SVC oxygen saturations as the patient transitioned from milrinone 0.375 µg/kg/min to probenecid 1,000 mg twice daily can be seen in [Figure 1](#).

DISCUSSION

Type 1 myotonic dystrophy is an autosomal dominant disorder associated with a cytosine-thymine-guanine trinucleotide repeat expansion in the untranslated region of the myotonic dystrophy protein kinase gene on chromosome 19 that affects multiple organ systems including the heart. RNA expressing these cytosine-uracil-guanine repeats sequesters muscle blind-like proteins, interfering with the splicing of RNAs that encode key sarcomere and calcium regulatory components. This leads to altered cardiomyocyte calcium homeostasis. Common cardiovascular manifestations

TABLE 1 Objective Measures With Probenecid Therapy

Hours From First Probenecid Dose	Milrinone (µg/kg/min)	Probenecid Dose	SVC Sat (% O ₂)	Fick Cardiac Output (BSA 1.7)	Fick Cardiac Index (Hb 12.0)	Heart Rate (beats/min)	Urine Output (ml/h)	Lactate (mmol/l)	Serum Creatinine (mg/dl)
-41	0.375	0	63.5	3.77	2.22	70	125	0.6	1.63
-24	0.250	0	34.4	2.18	1.28	102	100	1.9	1.66
-4	0.250	0	27.3	2.08	1.22	99	67	2.0	1.58
0	0.250	1g q12h	—	—	—	80	50	ND	ND
4	0.250	1g q12h	44.8	2.88	1.69	78	75	1.4	1.41
12	0.125	1g q12h	33.8	2.23	1.32	97	100	1.5	ND
21	0.125	1g q12h	54.0	3.62	2.12	77	85	0.5	1.30
28	0.000	1g q12h	44.9	3.23	1.91	92	62	0.6	ND
37	0.000	1g q12h	65.2	4.86	2.86	91	70	1.2	ND
51	0.000	1g q12h	43.8	3.16	1.86	87	75	1.6	1.77

BSA = body surface area; Hb = hemoglobin; ND = not done; O₂ = oxygen; Sat = saturation; SVC = superior vena cava.

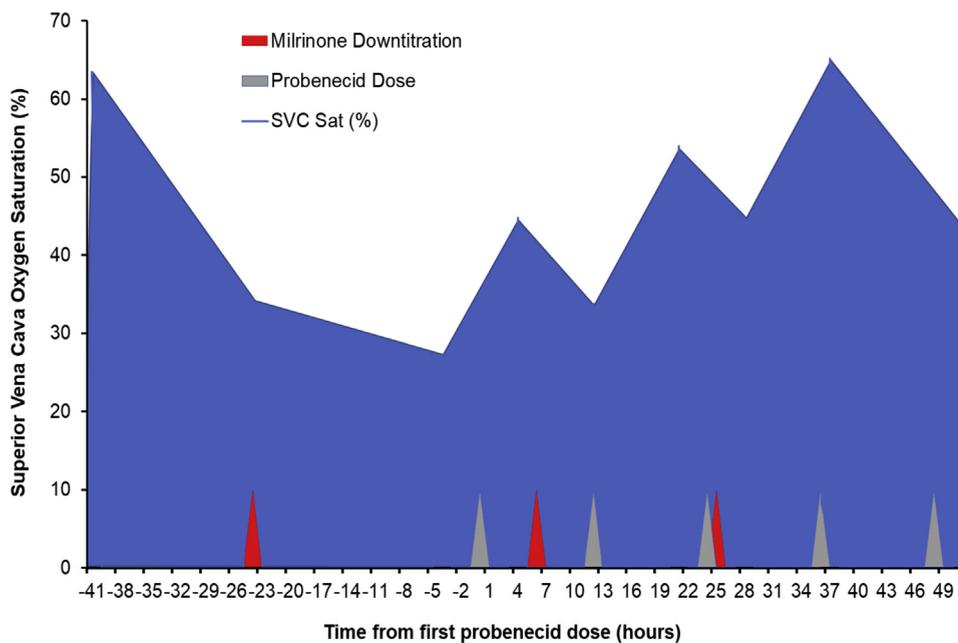
include supraventricular tachycardia (2,3), atrioventricular conduction block (2,3), bundle branch block (2,3), left ventricular hypertrophy (4), mitral valve prolapse (14%) (2,4), left ventricular systolic dysfunction (9% to 14%) (4,5), and sudden cardiac death (3).

Probenecid was initially developed in 1949, and because of its uric acid-lowering effects, it has historically been used for managing gout. However, recent data demonstrated that probenecid is a

relatively selective TRPV-2 calcium-channel agonist (1). Activation of the cardiomyocyte TRPV-2 channel in murine models leads to increased cytosolic calcium levels through a beta-adrenergic independent mechanism that involves increased sarcoplasmic reticulum loading and release of calcium ions (1).

Although myotonic dystrophy represents only a small fraction of potential heart failure causes, a preceding single-center trial of 20 stable outpatients

FIGURE 1 SVC Saturations Over Time



Change in the superior vena cava (SVC) saturation (Sat) over time in relation to intravenous milrinone down-titration (0.125 µg/kg/min increments) and 1,000-mg oral probenecid doses.

with either ischemic or nonischemic cardiomyopathy showed increased fractional shortening by echocardiography after 1 week of probenecid therapy regardless of disease origin (6). Additionally, probenecid has proven more effective than allopurinol in reducing cardiovascular events despite a similar lowering of uric acid levels (7). This finding suggests that probenecid exerts its cardioprotective effects through mechanisms independent of uric acid lowering.

This 56-year-old patient had multiple cardiac manifestations of advanced type 1 myotonic dystrophy, including nonischemic cardiomyopathy and mitral valve prolapse. Over the 12 years before presentation, he had slowly progressive mitral valve disease with worsening regurgitation, dilation of the left atrium and ventricle, and subsequent improvement in the calculated left ventricular ejection fraction to 60%. He was eventually referred for mitral valve replacement after New York Heart Association functional class III symptoms developed; however, the loss of a mitral regurgitant jet only unmasked his severe underlying cardiomyopathy.

After presenting in cardiogenic shock and realizing that he was not a candidate for advanced cardiac therapies because of the severity of his myotonic dystrophy, the patient expressed his desire for home hospice without intravenous therapies. A trial of probenecid therapy was proposed, given the pathophysiology for cardiomyocyte dysfunction in type 1 myotonic dystrophy (altered sarcomere function and calcium homeostasis) and the proposed activity of probenecid (increased sarcoplasmic reticulum loading and unloading of calcium). The probenecid dose of 1,000 mg twice daily was chosen because this was the dose used in the study by Robbins *et al.* (6) that showed benefit in patients with heart failure with reduced ejection fraction. With this dose of probenecid, intravenous inotropes were able to be successfully discontinued. We would recommend using this dose to optimize potential benefit until more detailed studies of dose and effect are performed.

Given this patient's goals of care, he was not managed with an indwelling Swan-Ganz catheter for accurate monitoring of hemodynamics and cardiac output and cardiac index. As a result, we were left with SVC oxygen saturation, serum lactate levels, serum creatinine levels, and hourly urine output as surrogate markers of cardiac output. The relationship between SVC and mixed venous oxygen saturation is

variable, with SVC oxygen saturation frequently overestimating mixed venous oxygen saturation during periods of cardiogenic shock (8). As a result, SVC oxygen saturation tends to overestimate cardiac output in patients with shock, and therefore use of this measure as a solitary marker of cardiac function may often underestimate a patient's burden of disease.

Taken together, the group of surrogate markers used in this case are helpful for a rough estimation of cardiac output. However, it is important to remember that cardiac output is dependent on the combination of preload, afterload, and myocardial contractility. Although pharmacology, animal models, and this case suggest that probenecid can improve myocardial contractility, these patients also require optimization of preload and afterload through aggressive diuresis and arterial dilation as tolerated. In this case, the patient was diuresed to a euvolemic state before the transition from milrinone to probenecid. He was unable to tolerate afterload reduction as a result of profound hypotension.

FOLLOW-UP

After the patient started probenecid, intravenous milrinone was discontinued without adverse sequelae. He briefly required repeat initiation of low-dose milrinone (0.125 µg/kg/min) after diuretic agents were held for 36 h, but he was eventually discharged to inpatient hospice, and he discontinued all intravenous therapies. He died 6 days after the second round of intravenous milrinone was stopped.

CONCLUSIONS

To the best of our knowledge, this case represents the first documented report of oral probenecid as a beta-adrenergic independent adjunctive therapy and eventual replacement for intravenous inotropes in end-stage heart failure from type 1 myotonic dystrophy. Although type 1 myotonic dystrophy represents the cause of only a small percentage of patients with heart failure, further studies have suggested that the findings of this case may be more widely applicable to patients with end-stage heart failure. Further study is warranted.

ADDRESS FOR CORRESPONDENCE: Dr. Evan C. Klein, Medical College of Wisconsin, 8701 Watertown Plank Road, Milwaukee, Wisconsin 53226. E-mail: evan.klein472@gmail.com.

REFERENCES

1. Koch SE, Gao X, Haar L, et al. Probenecid: novel use as a non-injurious positive inotrope acting via cardiac TRPV2 stimulation. *J Mol Cell Cardiol* 2012;53:134–44.
2. Phillips MF, Harper PS. Cardiac disease in myotonic dystrophy. *Cardiovasc Res* 1997;33:13–22.
3. Turner C, Hilton-Jones D. The myotonic dystrophies: diagnosis and management. *J Neurol Neurosurg Psychiatry* 2010;81:358–67.
4. Bhakta D, Lowe MR, Groh WJ. Prevalence of structural cardiac abnormalities in patients with myotonic dystrophy type I. *Am Heart J* 2004;147:224–7.
5. Wahbi K, Meune C, Becane HM, et al. Left ventricular dysfunction and cardiac arrhythmias are frequent in type 2 myotonic dystrophy: a case control study. *Neuromuscul Disord* 2009;19:468–72.
6. Robbins N, Gilbert M, Kumar M, et al. Probenecid improves cardiac function in patients with heart failure with reduced ejection fraction in vivo and cardiomyocyte calcium sensitivity in vitro. *J Am Heart Assoc* 2018;7:e007148.
7. Kim SC, Neogi T, Kang EH, et al. Cardiovascular risks of probenecid versus allopurinol in older patients with gout. *J Am Coll Cardiol* 2018;71:994–1004.
8. Lee J, Wright F, Barber R, Stanley L. Central venous oxygen saturation in shock: a study in man. *Anesthesiology* 1972;36:472–8.

KEY WORDS cardiogenic shock, cardiomyopathy, heart failure, inotropes, myotonic dystrophy, probenecid