

**Pulmonary hypertension associated with diazoxide:
the SUR1 paradox**

SUPPLEMENTAL TABLE 1. Summary of clinical cases reported in the literature of pulmonary hypertension associated with diazoxide use

	Article	Age at diagnosis	Sex	Associated cardiac abnormality or condition	Diazoxide dose (mg/kg/day)	Time to toxicity after starting diazoxide	Clinical symptoms	Type of exam	Hemodynamic	Treatment	Evolution
1	Silvani et al 2004 [1]	43 days infant	M	Premature infant	17	< 6 weeks	Respiratory failure, right heart failure	TTE	sPAP 55mmHg	High dosage furosemide, dopamine, dobutamine, captopril, ventilation, discontinuation of diazoxide	Improvement during the 5 days after withdrawal of diazoxide, extubation, reduction of Spap to 22 mmHg
2	Nebesio et al 2007 [2]	65 days infant	F	Laryngomalacia and obstructive apnea	13	4 weeks	Respiratory failure	TTE	severe right ventricular hypertrophy	Discontinuation of diazoxide	Complete resolution of PH 6 weeks after stopping the diazoxide
3	Yildizdias et al 2008 [3]	4 months	F	Premature infant	15	10 days	Respiratory failure, right heart failure	RHC	mPap 65mmHg, left ventricular end-diastolic pressure 12mmHg	High dosage furosemide, dobutamine, discontinuation of diazoxide	Respiratory and haemodynamic status dramatically improved in 6 days, reduction of Spap to 20mmHg
4	Demirel et al 2011 [4]	Around 15 days infant	M	None	15	6 days	Abdominal distension, vomiting, edema of the eyelids, tachycardia, and tachypnea	TTE	mPap 25mmHg and re-opening of ductus arteriosus	Digoxine, furosemide, fluid restriction, discontinuation of diazoxide	Clinical improvement in 24hours, reduction of Mpap to 20 mmHg at 24 hours and 16mmHg at 72

										hours with closure of the ductus arteriosus	
5	Timlin et al 2017 [5]	3 months infant	M	Premature infant	NA	10 weeks	Respiratory distress, poor distal perfusion	TTE	dilated right ventricle with elevated pulmonary pressures at 3/4 of systemic pressures	Oxygen, non-invasive ventilation, discontinuation of diazoxide	Improved with normalization of his echocardiogram in less than 12 days
6		3 days infant	M	Beckwith-Wiedemann Syndrome	12	3 days	Tachypnea, respiratory failure	TTE	Supra-systemic pulmonary artery pressures	Oxygen, inhaled NO, dexamethasone, discontinuation of diazoxide	Improvement in 30 days, normalization of pulmonary pressures
7		1 month infant	M	Premature infant	13	1 month	Abnormal pulmonary exam, hepatomegaly	TTE	dilation of all cardiac chambers, biventricular systolic dysfunction, pulmonary artery pressures at 2/3 of systemic pressures	Diuretics, hydrocortisone, discontinuation of diazoxide	Improvement after 6 days with normalization of pulmonary pressures
8	Herrera et al, 2018 [6]	6 days infant	NA	None	16	17 days	NA	TTE	pulmonary artery pressures at > 1/2 of systemic pressures, flattened ventricular septum	discontinuation of diazoxide	normalization of pulmonary pressures at 71 days
9		NA	NA	Large patent ductus arteriosus	15	NA	NA	TTE	pulmonary artery pressures	discontinuation of diazoxide	normalization of pulmonary

									at > 1/2 of systemic pressures, flattened ventricular septum		pressures at 100 days
10		54 days infant	NA	Large patent ductus arteriosus	6	29 days	NA	TTE	flattened ventricular septum	discontinuation of diazoxide	normalization of pulmonary pressures at 88 days
11		4 days infant	NA	Anomalous left coronary artery from the pulmonary artery	12	2 days	NA	TTE	pulmonary artery pressures at > 1/2 of systemic pressures, flattened ventricular septum	discontinuation of diazoxide	NA
12		19 days infant	NA	Ventricular septal defect	15	317 days	NA	TTE	flattened ventricular septum	discontinuation of diazoxide	NA
13		142 days infant	NA	patent ductus arteriosus after ligation	10	3 days	NA	TTE	pulmonary artery pressures at > 1/2 of systemic pressures	discontinuation of diazoxide	NA
14		NA	NA	patent ductus arteriosus after ligation	10	NA	NA	TTE	flattened ventricular septum	discontinuation of diazoxide	NA
15	Kylat et al, 2019 [7]	16 weeks	F	Extremely premature	15	9 days	Cardiorespiratory failure, opening of the ductus arteriosus	TTE	Near systemic pulmonary pressures	Mechanical ventilation, inotropic support, inhaled NO, discontinuation of diazoxide	Clinical improvement, TTE signs of PH resolved over two weeks. Death at 8

											months because of liver failure.
16	Thornton et al, 2019 [8]	NA	NA	Atrial septal defect	7	42 days	NA	TTE	NA	NA	NA
17		NA	NA	Small ventricular septal defect	8	13 days	NA	TTE	NA	NA	NA
18		NA	NA	Small ventricular septal defect, bicuspid aorti valve	3	105 days	NA	TTE	NA	NA	NA
19		NA	NA	Patent ductus arteriosus discovered after dg of PH	15	5 days	NA	TTE	NA	NA	NA
20		NA	NA	Patent ductus arteriosus discovered after dg of PH	9	4 days	NA	TTE	NA	NA	NA
21		NA	NA	Hypoplastic pulmonary valve, patent ductus arteriosus	12	22 days	NA	TTE	NA	NA	NA
22		NA	NA	Patent ductus arteriosus	12	5 days	NA	TTE	NA	NA	NA
23		NA	NA	Patent ductus arteriosus	2	55 days	NA	TTE	NA	NA	NA
24	Ohnishi et al, 2020 [9]	20 weeks	M	Beckwith-Wiedemann Syndrome	11,5	30 days	Mild respiratory distress and poor sucking	RHC	Mpap 58mmHg, left PAWP 18mmHG, right PAWP, 19mmHg PVR 6.6 WU, left ventricular end-diastolic pressure 18mmHg	Oxygen, diuretics, sildenafil, decrease of the dose of diazoxide then stop	4 months after, Mpap 21 mmHg, left PAWP 12mmHG, right PAWP, 10mmHg PVR 0.9 WU, left ventricular end-diastolic pressure 12mmHg

25	Sotiridou et al, 2021 [10]	12 weeks	M	Tyrosinaemia type 1, neonatal liver failure	12	14 days	Signs of PH	TTE	NA	Continuous positive airway pressure, sildenafil and furosemide. Discontinuation of diazoxide	TTE normal at 9 months
26	Sullivan et al, 2021 [11]	3 weeks	M	Non compaction cardiomyopathy, chromosomal translocation	NA	7 days	Lethargy and hypoxia	TTE	with severe right atrial and ventricular dilation, interventricular septal flattening, mild right ventricular hypertrophy	Oxygen, discontinuation of diazoxide	Improvement of PH at 3 days, normalisation at nine months
27	Salguero et al, 2022 [12]	14 weeks	F	Kabuki syndrome (mutation in <i>KDM6A</i> gene), hypoplastic aortic arch, patent ductus arteriosus, patent foramen ovale, and a perimembranous ventricular septal defect	5	NA (Between 4 to 10 weeks)	Sepsis, Hypoxia and right heart failure	TTE	Severe PH and decreased biventricular function with pericardial effusion	Veno-arterial ECMO, diuretics, pericardiocentesis, NO, invasive ventilation, discontinuation of diazoxide, low dose sildenafil	ECMO weaned off within 3 days, TTE normal at 2 weeks
28	Newman-Lindsey, 2022 [13]	12 weeks	M	Premature infant, Dubin-Johnson syndrome, patent ductus arteriosus transcatheter closure	10	14 days	NA	TTE	sPAP 78 mmHg	Conventional ventilator with inhaled nitric oxide	Recovered after 4 weeks on ventilator and 7 weeks on inhaled nitric oxide, discharged at 52 weeks corrected gestational age

29		8 weeks	F	Premature infant, twin, laryngomalacia requiring supraglottoplasty.	6.5	13	NA	TTE	RV systolic pressure at least 77.8mmHg plus RA pressure. IV septum severely flattened throughout cardiac cycle. Moderate dilation and mild hypertrophy of RV.	High Flow Nasal Cannula, inhaled nitric oxide	Recovered and returned to room air 10 weeks after diazoxide. Discharged at 48 weeks corrected gestational age.
30		3 weeks	M	Premature infant, ambiguous genitalia with XY karyotype	10	7	NA	TTE	Moderate patent ductus arteriosus predominantly right to left shunt. IV septum moderately flattened throughout cardiac cycle.	Intubation and high frequency oscillatory ventilation, inhaled nitric oxide. Hypoxic respiratory failure leading to ECMO.	Demise during ECMO, related to pulmonary hypertensive crisis
31		1 week	M	Premature infant, deletion of Recurrent Proximal 1q21.1 Region	10	4	NA	TTE	RV systolic pressure at least 74mmHg plus RA pressure.	CPAP	Recovered and discharged on room air.

CPAP : continuous positive airway pressure ; ECMO: extracorporeal membrane oxygenation; F: female; M: male; PAP: mean pulmonary artery pressure; NA: non available; RHC: right heart catheterization; PAWP : Pulmonary artery wedge pressure ; PH: pulmonary hypertension ; RA: right atrium ; RV : right ventricular ; TTE: transthoracic echocardiography ; sPAP : systolic pulmonary artery pressure

Supplemental Table 2. Characteristics of cases reported with diazoxide in the WHO pharmacovigilance database. (PT: MedDRA Preferred Term)

Characteristics	Number of cases (n=61)
Age	
0-23 months	50
2-11 years	2
>75 years	2
Unknown	7
Sex	
Female	31
Male	30
Evolution	
Died	2
Not recovered	5
Recovered with sequelae	1
Recovering	7
Recovered	29
Evolution Unknown	17
Seriousness	
Yes	57
No	1
Serious unknown	3
Reported symptoms	
PT: Pulmonary hypertension	43
PT: Pulmonary arterial hypertension	14
PT: Right ventricular failure	3
PT: Tricuspid valve incompetence	2
PT: Right ventricular hypertrophy	2
PT: Pulmonary vein stenosis	1
PT: Right ventricular dysfunction	1

PT: Right atrial dilatation	1
Top associated symptoms	
Co-PT1	Respiratory distress 4/61
Co-PT2	Respiratory failure 3/61
Co-PT3	Condition aggravated 3/61
Co-PT4	Dyspnoea 2/61
Co-PT5	Cardiac failure congestive 2/61
Country of reporting	
Country 1	United Kingdom of Great Britain
Country 2	United States of America - 18 / 61
Country 3	France - 14 / 61
Country 4	Canada- 4 / 61
Country 5	Japan - 2 / 61

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