

Overreliance link between asthmatic subjects and short-acting β_2 agonists

A B S T R A C T

In this brief communication, it was described the overreliance link generated between a young asthmatic subject and Short Acting Beta agonist (SABA) bronchodilator. It was an attempt to delineate the stages of this conflicting link where predominated the overreliance on SABA that might be one of the main circumstances surrounding near fatal asthma attack. New approach is needed from international guidelines to avoid development of such a problematic link between asthmatic subjects and SABA.

JEB was 16 yrs old when a saving endotracheal intubation was performed after arrival to the hospital in respiratory arrest due to near fatal asthma attack. He had asthma diagnosis since he was 2 years old. A month before, he came to the Emergency Room with severe acute asthma and he also had a prior near fatal asthma event with hypercapnia and arterial pH = 7.12 without respiratory arrest. At the last admission, arterial blood gas analysis, vital signs and peripheral vein access was obtained while the initial support with breathing bag and high oxygen flow preceded the endotracheal intubation. Respiratory acidosis was confirmed with arterial pH = 7.03 and PaCO₂ = 99 mm Hg. He was the subject number 5 at Table 1 [1]. After 7 hours of mechanical ventilation and 24 hours of hospitalization we registered an FEV₁ of 66% predicted. (Tables 1 and 2). Then the adolescent escaped from the hospital. This behaviour was one of the features of difficult to treat asthma. He had consumed more than 2 canister of SABA the week before admission. It is not rare, that clinicians evoked the simplistic direct cause-effect relationship of SABA overuse and death from cardiac toxicity in asthma [2,3]. The above mentioned manuscript of the New Engl J Med supported the hypothesis of asphyxia against cardiac events related to death from asthma [1]. The relationship between increased SABA consumption and increased in mortality rate from asthma was by far not associated with cardiac adverse events. It was recognised that β_2 agonists as a drug class had the potential for long-term adverse effects, increasing asthma severity through enhanced bronchial hyperresponsiveness and reduced lung function [2–4]. Also; it was shown that SABA overreliance delayed recognition of life threatening attack [2–4].

Now, it is pertinent to describe three stages of SABA use in this subject. At stage one he began using SABA PRN, probably less than 2 puffs per week and the third stage when SABA was the life-saving bronchodilator until arriving hospital. The second stage could be denominated the wasting window of opportunity because he did not step up asthma treatment and the overreliance link between SABA and him had been definitively installed. Fortunately, these circumstances are uncommon nowadays; but the ways for developing high risk and life threatening asthmatic exacerbation continues open. Most of the asthmatic populations are being managed by general practitioners at the beginning of the disease and most of the patients receive SABA as the only pharmacologic agent. “JEB” developed a strong overreliance link with SABA as a false key treatment with excessive over-use and hence a progressive and detrimental disease course; with delay in seeking help

that finished with respiratory arrest. Physio-pathologically, respiratory arrest was a consequence of only and partially treating bronchoconstriction and not treating inflammation. Asthmatic subjects tended to abandon ICS because of lack of immediate bronchodilator action and symptom relief; and they were prone to use SABA instead. The steps presentation of the different guidelines for asthma management and treatment might be misinterpreted as sequential visits, for recent asthma diagnosis or suspected asthma that would correspond to step one [5,6]. Every patient whatever the severity was erroneously initiated treatment from step one (only SABA PRN). For GINA, first option step one was kept blank in Fig. 2; then most of the asthmatic subjects receive SABA as the first and unique prescription [5]. This issue may be potentiated by reluctance to use ICS due to corticophobia that was dragged as an original sin from the time of chronic and systemic corticosteroid therapy.

The low quotient ICS/SABA that we are already seeing in many countries has many protagonists: 1) Health regulatory authorities only viewed the direct costs of pharmacologic intervention; when there's a large body of evidence in favour of ICS for reduction asthma morbidity and mortality. 2) Physicians and paediatricians oversize the risk of adverse events of ICS, when ICS are one of the most safe and effective pharmacologic agents for asthma, even in pregnancy. 3) Patients loose confident in ICS because of the lack of SABA-like, rapid bronchodilation. 4) International recommendations like GINA, keep blank the first treatment step fomenting prescription of SABA; with the exception of the BTS/SIGN [6] recommendations as it was pointed out [7]. 5) Finally, lack of continuing educational program for all the parts involved in asthma management.

Getting back to the patient JEB; he never returned to the hospital. Adolescence is a great obstacle for adherence. It could be speculated that if he used ICS at the stage two described above instead of SABA; he had not suffered a respiratory arrest. Even more, if SABA never had been prescribed his outcome might be better; but what would be the therapeutic options?

If the eradication of SABAs is raised; which alternatives to SABAs exists if any? GINA recommended ICS&formoterol as maintenance and relief for steps 3 to 5 [5]. O'Byrne and colleagues proposed a drastic change with combined ICS plus SABA or rapid LABA&ICS all along the different steps by eradicating SABA as relief medication [8]. The approach for adolescents at step one of GINA or with initial mild asthma

Table 1General Characteristics of All Patients and Their Outcomes.^a With permission from New Engl J Med.

Patient No.	Age	Sex	Duration of Asthma	Duration of Symptoms	MV	PaCO ₂ after Weaning	Hospital Stay	FEV ₁ , at Discharge
	yr		yr	hours		mm fig	days	liters (% of predicted) ^b
1	32	p	3	360	16	35	6	2.29 (82)
2	24	M	21	6	12	33	6	3.82 (96)
3	32	F	28	7	51	37	9	2.07 (70)
4	16	F	13	72	7	36	3	1.96 (65)
5	16	M	14	24	7	32	1	2.24 (66)
6	21	M	20	168	15	37	8	2.73 (66)
7	27	M	26	4	7	35	3	2.73 (63)
8								
1st admission	49	M	29	72	6	39	3	2.78 (96)
2nd admission	49	M	29	12	12	36	3	2.56 (88)
9	35	F	9	24	9	30	8	2.40 (73)
10	38	M	33	48	63	31	10	2.73 (78)
Mean	30.8	—	20.5	24 ^c	12 ^c	34.6	5.5	2.6 (76.6)
SD	11.5	—	9.6	65 ^d	9 ^d	2.8	3.0	0.5 (12.3)

^a MV denotes mechanical ventilation, and PaCO₂ partial pressure of arterial carbon dioxide.^b Predicted values are from Morris et al.²³^c Median.^d Interquartile range.**Table 2**Findings at the Time of Respiratory Arrest.^a With permission from New Engl J Med.

Patent No.	Heart Rate	Blood Pressure		pH	PaCO ₂	PaO ₂	HCO ₃	Method of Ventilation ^b	SERum Potassium	Paw
	beats/min	Systolic	Diastolic							
		mm Hg				mm Hg	mmol/liter		mmol/liter	cm of water
1	167	too	80	NR	NR	NR	NR	B bag	NR	45
2 ^c	150	NR	NR	6.94	92	410	18	T tube	3.5	44
	125	140	70	7.01	100	200	24	B bag	3.6	77
4	120	120	90	7.13	69	260	22	T tube	NR	NR
5	150	160	110	7.03	99	190	24	B bag	3.3	40
6	150	NR	NR	6.93	143	143	27	B bag	3.9	60
7	40	160	300	6.87	92	99	16	T tube	NR	70
8										
1st admission	136	170	100	6.87	155	106	26	T tube	3.1	48
2nd admission	167	170	105	7.19	62	270	23	B bag	3.8	70
9	120	200	100	7.00	96	73	22	B bag	3.0	45
10	150	180	100	7.11	63	123	19	B bag	3.1	70
Mean ± SD	134.1 ± 35.4	156 ± 30.9	95 ± 12.7	7.01 ± 0.11	97.1 ± 31.1	187.4 ± 103.0	22 ± 3.5	—	3.4 ± 0.3	56.9 ± 13.9

^a PaCO₂ denotes partial pressure of arterial carbon dioxide, PaO₂ partial pressure of arterial oxygen, HCO₃ bicarbonate, Paw peak airway pressure, and NR not recorded.^b Hyperoxic gas mixtures were administered by T tube or breathing bag-mask (8 bag),^c Patient 2 had atrial fibrillation.

might be ICS alone or rapid LAB/ICS as needed.

In the era of biologic agents and personalized medicine; it is absurd to get back discussion to SABA overuse; but biologic asthma target is less than 5% of all asthmatic subjects and SABA are used by almost all the asthma population. The overreliance connecting link created between asthmatic subjects and SABA is the responsible of the worse outcome. Which circumstances are behind this link? 1) SABA is the first pharmacologic agent that is prescribed to almost all. 2) SABA does not have anti-inflammatory action. 3) Subjects enter a sort of upward spiral of SABA consumption. 4) At the expense of true maintenance asthma treatments. 5) Finally, SABA should not be considered as a treatment for chronic asthma [7].

References

- [1] N.A. Molino, L.J. Nannini, N.A. Martelli, A.J. Slutsky, Respiratory arrest in near fatal asthma, *N. Engl. J. Med.* 324 (1991) 285–288.
- [2] J. Crane, N. Pearce, C. Burgess, R. Beasley, Asthma and the β agonist debate, *Thorax* 50 (suppl 1) (1995) S5–S10.
- [3] L.J. Nannini Jr., Morbidity and mortality from acute asthma, *At the book (Chapter 2)*, in: J. Hall, T. Cordbridge, G. Rodrigo, C. Rodrigo (Eds.), *Acute Asthma: Assessment and Management*, McGraw Hill, New York, NY, USA, 2000, pp. 11–27 (ISBN = 0-07-026026-5).
- [4] R. Beasley, N. Pearce, J. Crane, C. Burgess, Beta agonists: what is the evidence that their use increases the risk of asthma morbidity and mortality? *J. Allergy Clin. Immunol.* 103 (suppl) (1999) S18–S30.
- [5] GINA Executive Committee, Global Strategy for Asthma Management and Prevention, Global Initiative for Asthma (GINA), (2017) www.ginasthma.org Date last accessed: March 16, 2017.
- [6] British Thoracic Society/Scottish Intercollegiate Guidelines Network, British Guideline on the Management of Asthma: a National Clinical Guideline, (2016) www.brit-thoracic.org.uk Date last accessed: April 10, 2017.
- [7] L.J. Nannini, N.S. Neumayer, Step one treatment for asthma should not be left blank and SABA-alone might not be a treatment option for asthma Step 1, *Respiration* 95 (3) (2018) 212–214.
- [8] P.M. O'Byrne, C. Jenkins, E.D. Bateman, The paradoxes of asthma management: time for a new approach? *Eur. Respir. J.* 50 (2017) 1701103.

Luis J. Nannini

Chief Pulmonary Section, Hospital de G Baigorria, Universidad Nacional de Rosario, Argentina

E-mail address: ljnannini@hotmail.com