FACULTY OF MEDICINE AND HEALTH SCIENCES

Which factors can importantly influence management of nocturia and can improved definitions of nocturnal polyuria benefit interventions?

Tine Kold Olesen

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Summary of research

Introduction

Nocturia (waking up to void at night) is associated with multiple causes and stages of disease, and often multiple causes can co-exist within the same patient. Nocturia symptoms can be expressed mechanistically as an imbalance between nocturnal diuresis and functional bladder capacity (FBC) overnight. Reduced FBC due to e.g., overactive bladder or benign prostate enlargement increases the likelihood of nocturia. For excessive nightly urine production (nocturnal polyuria [NP]), the causes may be related to disturbances in hormones, congestive heart failure, hypertension, sleep apnoea, or renal insufficiency.

Research

In a systematic literature review, we evaluated the suggested diagnostic definitions and we found that these definitions of NP were based on limited data and when evaluated by independent study cohorts, they performed poorly. These findings illustrate the inconclusive nature of current NP definitions. We then applied a pragmatic approach by testing predictive modelling (machine learning technique) to determine which independent variables contribute to discriminating patients with clinically significant nocturia from those with no or mild nocturia. As data source we used data from patient voiding diaries and individual factors such as age, BMI, and gender at birth. The first model was a post hoc analysis of existing data as a pilot study. The model showed an excellent fit. We applied the same technique to a much bigger data set. A dataset of 1479 patients (males/females with a broad age span). We tested the same factors as in the previous smaller model and concluded that the nocturnal urine production per hour (NUPh) in combination with sleep duration, and FBC had excellent performance. Factors such as 24-hour urine output, fluid intake, age, gender at birth and race played a less important role. The final aim was to test the predictive modelling in treatment response to an antidiuretic to enable better clinical management. Unfortunately, the desired results could not be met. The observed negative result can be related to the selection of our primary endpoint, the working mechanism of the antidiuretic and/or potential high impact of noninterventional changes in patient behavior.

Promotors:

Professor Karel Everaert, Urology Department, Sector MVK Chairman, Ghent University Hospital. Department of Human Structure and Repair, Ghent University

Professor Johan Vande Walle, Internal Medicine and Paediatrics Department, Ghent University Hospital. Faculty of Medicine and Health Science

A possible limitation of my work is that the results were based on retrospective analysis of data generated from prospectively accrued clinical trial cohorts. However, due to considerable ambiguity regarding prior definitions of NP and factors which importantly influence nocturia, this field of research was relying on data from many cohorts with small sample sizes that were not possible independently replicate or validate in other studies. My research has been based on a considerate use of resources, in this case existing large databases, which had not been used before to clarify whether a predictive model would be of clinical value, and whether we could identify a definition of NP, or reject definitions of NP that would not provide any clinical value before embarking on a large prospective study.

Clinical application

My data show that machine learning technique can be used in this research field but will require more data collection including the development of an 'app' for full usability. The modelling is complicated, and software programming is warranted.

Near term application of my research findings are:

1) A requirement of a comprehensive diagnosis process to identify the patho-physiology of nocturia.
2) A recommendation to use the NUPh definition for excessive nightly urine production and focus less on other definitions in the public domain.
3) For certain risk patients it may be beneficial to identify the nature of the excessive urine production, recognizing a complicated process.
4) An anti-diuretic may be tested for a trial period and outcome measured as holistic patient benefit.

Examination committee:

Prof. dr. Johan Van de Voorde
Chair Faculty of Medicine and Health Sciences Ghent University, Belgium.

Prof. dr. Ann Raes Secretary Faculty of Medicine and Health Sciences Ghent University, Belgium.

Prof. dr. Jens Peter Norgaard Faculty of Medicine and Health Sciences Ghent University, Belgium.

Dr. Lien Dossche, Internal Medicine and Paediatrics Department, Ghent University Hospital, Belgium.

Dr. François Hervé, Department of Urology, Ghent University Hospital and University Clinic, Saint Luc, Brussels, Belgium.

Dr. Kristian Vinter Juul, Medical Science, Ferring Pharmaceuticals, Copenhagen, Denmark.

Dr Salvador Arlandis, University Hospital I Polytechnic la Fe, Valencia, Spain.

Financing:

No financing obtained.

Short CV:

Current position (FEB2020-current):
Vice President, Program and Alliance Management, Alvotech. My principal responsibilities are: Directing programs for biosimilars from identification of clone to pre-launch. Establish new processes for cross functional development.

Previous position (FEB2001-JAN2020):
Senior Director, Project and Portfolio Management, Research and Development, Ferring Pharmaceuticals. My principal responsibilities were:
Directing programs for novel molecular entities from preclinical research to first in man studies and comprehensive clinical development followed by regulatory submission and approval within the field of urology/oncology.

Educational Background:
MBA, Imperial College, London 2012
M.Sc. (Pharm.) Copenhagen University, 1992

Full text available at:

CONTACT
Tine.KoldOlesen@ugent.be or
tinekoldolesen@gmail.com
www.ugent.be

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