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Stochastic model for finding the Gallbladder Ejection fraction results

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Abstract
The purpose of this paper was to evaluate the use of a commercially available lactose free fatty meal food supplement, as an alternative to sincalide cholescintigraphy, to develop a standard methodology. The second order linear homogeneous differential equation was used to determine the normal gallbladder ejection fractions results for this supplement.

Keywords: Gallbladder Ejection Fraction, Cholecystokinin (CCK), Gamma Distribution.

1. Introduction

Sincalide is routinely used for various indications in conjunction with cholescintigraphy. One common indication is to evaluate the adequacy of gallbladder contraction and to calculate a gallbladder ejection fraction (GBEF) in order to confirm or exclude the preoperative diagnosis of chronic acalculous cholecystitis [3] & [9]. However, sincalide was not in production or available between November 2001 and December 2002. Alternative methods for evaluating gallbladder contraction became necessary.

Fatty meals have been used by investigators and clinicians over the years to evaluate gallbladder contraction in conjunction with oral cholecystography, ultrasonography, and cholescintigraphy. Proponents assert that fatty meals are physiologic and low in cost. Numerous different fatty meals have been used. Many are institution specific. Methodologies have differed, and few investigations have studied a sufficient number of subjects to establish valid normal GBEFs for the specific meal. Whole milk and half and half have the advantage of being simple to prepare and administer [1], [2] & [8]. Milk has been particularly well investigated. Large numbers of healthy subjects have been studied, a clear methodology described, and normal values determined [8]. However, lactose intolerance is common and is associated with quite disagreeable symptoms. A commercially available standardized, prepackaged lactose free meal would have advantages for clinical practice.

In this paper, the model is characterized by the Markov Property of entering and exiting processes, by the service channel and by the system capacity to accommodate one customer at a time [4], [5], [6] and [7]. Here we use the function $e(t)$ satisfies the second order linear homogenous differential equation

$$q(t) = \frac{\lambda^2}{A} e^{-\left(Bt/2\right)} \left[e^{\left(At/2\right)} - e^{-\left(At/2\right)} \right]$$

Where

$$A = \sqrt{\mu(4\lambda + \mu)}, B = (2\lambda + \mu)$$

2. Mathematical Model

Let P_0 be a point on the equator of a three dimensional sphere. Let us assume that the particle starts moves from P_0 along the equator in one of the two possible directions (clockwise or counter clockwise) with velocity c.

At the first Poisson event (occurring at time T_1) it starts moving on the meridian joining the north pole P_N with the position reached at time T_1 (denoted by P_1) along one of the two possible directions.

At the second Poisson event the particle is located at P_2 and its distance from the starting point P_0 is the length of the hypotenuse of a right spherical triangle with cathetus P_0P_1 and P_1P_2; the hypotenuse belongs to the equatorial circumference through P_0 and P_2.
Now the particle continues its motion (in one of the two possible directions0 along the equatorial circumference orthogonal to the hypotenuse through P_0 and P_2 until the third Poisson event occurs.

In general, the distance $d(P_0P_1)$ of the point P_1 from the origin P_0 is the length of the shortest arc of the equatorial circumference through P_0 and $P_1$and therefore it takes values in the interval $[0,\pi]$. Counter clockwise motions cover the arcs in $[-\pi,0]$ so that the distance is also defined in $[0,\pi]$ or in $[-\pi/2,\pi/2]$ with s shift that avoids negative values for the cosine.
By means of the spherical Pythagorean relationship we have that the Euclidean distance $d(P_0P_2)$ satisfies

$$\cos d(P_0P_2) = \cos d(P_0P_1)\cos d(P_1P_2)$$

and, after three displacements,

$$\cos d(P_0P_3) = \cos d(P_0P_2)\cos d(P_2P_3)$$
$$= \cos d(P_0P_1)\cos d(P_1P_2)\cos d(P_2P_3)$$

After n displacement the position P_t on the sphere at time t is given by

$$\cos d(P_0P_t) = \prod_{k=1}^{n}\cos d(P_kP_{k-1})\cos d(P_nP_t)$$

Since $d(P_kP_{k-1})$ is represented by the amplitude of the arc run in the interval (t_k,t_{k-1}), it results

$$d(P_kP_{k-1}) = c(t_k,t_{k-1})$$

The mean value $Q\{\cos d(P_0P_t)\,|\,N(t)=n\}$ is given by

$$Q_n(t) = Q\{\cos d(P_0P_t)\,|\,N(t)=n\}$$
$$= \frac{n!}{t^n}\int_0^t dt_1\int_{t_1}^t dt_2 \ldots \int_{t_{n-1}}^t dt_n \prod_{k=1}^{n+1}\cos c(t_k,t_{k-1})$$
$$= \frac{n!}{t^n}H_n(t)$$

Where $t_0=0, t_{n+1}=t$ and

$$H_n(t) = \int_0^t dt_1\int_{t_1}^t dt_2 \ldots \int_{t_{n-1}}^t dt_n \prod_{k=1}^{n+1}\cos c(t_k,t_{k-1})$$

The mean value $Q\{\cos d(P_0P_t)\}$ is given by

$$Q(t) = Q\{\cos d(P_0P_t)\}$$
$$= \sum_{n=0}^{\infty} Q\{\cos d(P_0P_t)\,|\,N(t)=n\}Pr\{N(t)=n\}$$
$$= e^{-\lambda t}\sum_{n=0}^{\infty}\lambda^n H_n(t)$$

By steps similar to those of the hyperbolic case we have that $H_n(t), t \ge 0$, satisfies the difference differential equation

$$\frac{d^2}{dt^2}H_n = \frac{d}{dt}H_{n-1} - c^2 H_n$$

where $H_0(t) = \cos ct$and therefore we can prove the following:

The mean value $Q(t) = Q\{\cos d(P_0P_t)\}$ satisfies

$$\frac{d^2}{dt^2}Q = -\lambda\frac{d}{dt}Q - c^2 Q \qquad (1)$$

with initial conditions

$$\begin{cases} Q(0) = 1 \\ \frac{d}{dt}Q(t) = 0 \end{cases} \qquad (2)$$

and has the form

$$Q(t) = \begin{cases} e^{-\frac{\lambda t}{2}}\left[\cosh\frac{Ct}{2} + \frac{\lambda}{\sqrt{\lambda^2-4c^2}}\sinh\frac{Ct}{2}\right] & 0 < 2c < \lambda \\ e^{-\frac{\lambda t}{2}}\left[1+\frac{\lambda t}{2}\right] & \lambda = 2c > 0 \\ e^{-\frac{\lambda t}{2}}\left[\cosh\frac{Dt}{2} + \frac{\lambda}{\sqrt{4c^2-\lambda^2}}\sinh\frac{Dt}{2}\right] & 2c > \lambda > 0 \end{cases} \qquad (3)$$

Where $C = \sqrt{\lambda^2-4c^2}, D = \sqrt{4c^2-\lambda^2}$

The solution to the problem (1) and (2) is given by

$$Q(t) = \frac{e^{-\frac{\lambda t}{2}}}{2}\left[\left(e^{\frac{ct}{2}} + e^{-\frac{ct}{2}}\right) + \frac{\lambda}{c}\left(e^{\frac{ct}{2}} - e^{-\frac{ct}{2}}\right)\right] \qquad (4)$$

So that (3) emerges [4] & [7].

For large values of λ, the first expression furnishes $Q(t)\sim 1$ and therefore the particle hardly leaves the starting point. If $\frac{\lambda}{2} < c$, the mean value exhibits an oscillating behavior; in particular, the oscillations decrease as time goes on, and this means that the particle moves further and further reaching in the limit the poles of the sphere. In view of (4), we can prove the following.
In [7], The functions

$$Q(t) = \int_s^t dt_1 \ldots \int_{t_{n-1}}^t dt_n e^{-\mu(t-t_n)}\prod_{i=1}^{n}\left[1-e^{-\mu(t_i-t_{i-1})}\right]$$

with $t_0 = s$ do not depend on t but on the time interval $[s,t)$.

$$Q^{(s,n,1)}(t) - Q^{(0,n,1)}(t-s) \qquad (5)$$

The functions

$$Q^{(0,n,1)}(t) = \int_0^t dt_1 \ldots\ldots \int_{t_{n-1}}^t dt_n e^{-\mu(t-t_n)}\prod_{i=1}^{n}\left[1-e^{-\mu(t_i-t_{i-1})}\right]$$

satisfy the difference differential equations

$$\frac{d^2}{dt^2}Q^{(0,n,1)}(t) - -\mu\frac{d}{dt}Q^{(0,n,1)}(t) + \mu Q^{(0,n-1,1)}(t)$$

where $t_0 = 0, t > 0, n \geq 1$ (6)

The functions
$Q^{(0,n,0)}(t) = \int_0^t dt_1 \ldots \int_{t_{n-1}}^t dt_n e^{-\mu(t-t_n)} \prod_{i=2}^n [1 - e^{-\mu(t_i - t_{i-1})}]$

satisfy the differential equations

$$\frac{d^2}{dt^2} Q^{(0,n,0)}(t) = -\mu \frac{d}{dt} Q^{(0)}_{n,0}(t) + \mu Q^{(0,n-1,0)}(t)$$

where $t > 0, n \geq 1, Q^{(0,n,0)}(0) = 0$ (7)

In view of (7) we can prove the following,

The function $q(t)$ satisfies the second order linear homogenous differential equation

$$q(t) = \frac{\lambda^2}{A} e^{-(Bt/2)} \left[e^{(At/2)} - e^{-(At/2)} \right]$$

Where $A = \sqrt{\mu(4\lambda + \mu)}, B = (2\lambda + \mu)$ (8)

3. Example

Twenty healthy paid volunteers (7 Men & 13 Women) were studied. They ranged in age from 21 to 47 years and weighed 59.8 – 94.5 kg. All had negative medical histories for hepatobiliary and gallbladder disease, had no personal or family history of hepatobiliary disease, and was not taking any medication known to affect gallbladder emptying. Before the study, all underwent gallbladder/hepatobiliary ultrasonography, screening blood tests including complete blood cell count, comprehensive metabolic profile, and urinalysis. The subjects fasted for 4 –12 hours before cholescintigraphy. Mebrofenin was injected intravenously with the patient supine. Conventional cholescintigraphy was performed for 1 hour using a large field of view single head gamma camera and a low energy, all purpose, parallel whole collimator, Gallbladder filling occurred by 60 minutes in 19 of 20 subjects.

After voiding, the 19 subjects ingested a 240 ml can of the supplement while sitting. Meal composition was identical regardless of non-nutritional flavoring. Patients again lay supine, and images were acquired for 60 minutes on a computer. Computer processing was performed in a manner similar to that described previously by us for sincalide cholescintigraphy [2] & [8]. On the computer display, regions of interest were drawn for the gallbladder and adjacent liver. Background and decay corrected time activity curves were generated. GBEFs were calculated using the maximum counts minus the minimum counts divided by the maximum counts.

The GBEF data had a non-Gaussian distribution. Because of this and the number of subjects studied, an ad hoc method of statistical analysis was created. The smallest of GBEF observations is an estimate of the 5.6% point of the distribution; however, the lowest data value observed in the tail of the distribution may be unstable. To obtain a better estimate of the lower 5^{th} percentile (5% point), the data were compared with a normal distribution and with an empiric model that fit a cubic polynomial to the cumulative distribution of GBEF. The normal distribution was systematically biased, whereas the cubic polynomial provided a nearly perfect fit over the limited data range. The estimated percentile that we report is the model based, predicted GBEF value when the cumulative distribution is at 5% [9].

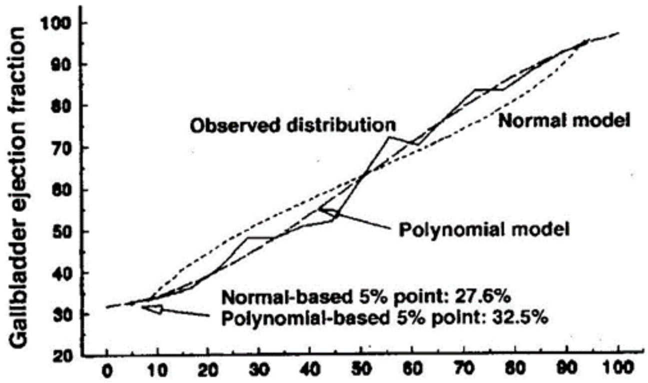
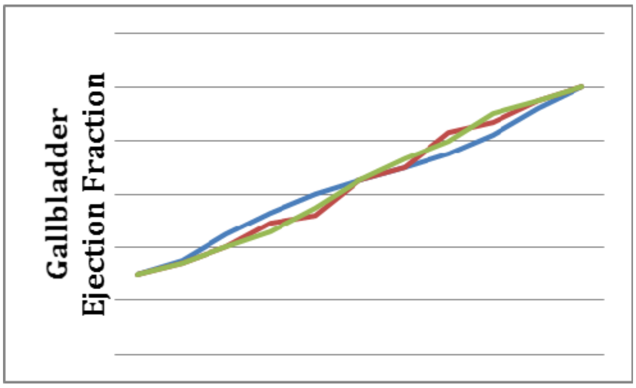


Fig (1): Cumulative distribution of GBEF observations for study subjects



Blue Line: Normal Model
Green Line: Polynomial Model
Red Line: Observed Distribution
Fig (2): Cumulative distribution of GBEF observations for study subjects
(Using Gamma Distribution)

4. Conclusion

The medical report suggests a standard methodology and normal gallbladder ejection fractions (GBEFs) were established for Supplement stimulated cholescintigraphy. The medical reports {Figure (1)} are beautifully fitted with the mathematical model {Figure (2)}; (i.e) the results coincide with the mathematical and medical report.

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