Event-History Data Problems in Differential Diagnosis: Clinical Applications from Apudoma-Caused Hypertension

A.L. Long, PhD

International Network Services

H.H. Whitman III, MD, FACP, FACR

New York Presbyterian – Weill Cornell Medical Center for Hypertension; Summit Medical Group, Chief, Department of Rheumatology ; and Hospital for Special Surgery

C.J. Gelber, MD

Summit Medical Group, Chief, Department of Nephrology

June 7, 2006

Event-history data on hypertension: Differential diagnosis of apudoma?

- **Primary HPT (90%)**
- **Bilateral renal parenchymal disease (5%)**
  - ***Chronic glomerulonephritis***
  - ***Interstitial nephritis***
  - ***Polycystic disease***
  - ***Diabetic nephropathy***
  - ***Systematic lupus erythematosus***
  - ***Amyloidosis***
  - ***Multiple myeloma***
  - ***Scleroderma***
  - ***Wegener's granulomatosis***
  - ***Goodpasture's disease***
  - ***Periarteritis nodosa***
  - ***Takayasu's arteritis***
  - ***Vasculitis***
  - ***Balkan nephritis***
  - ***Congenital renal disease***
- ***Italics = Have no catecholamine and/or other metabolite excess***
- **Starred = May have paroxysmal HPT**
- **Red = Apudoma (amine precursor update and decarboxylation) cells**

- **Other diastolic HPT causes (5%)**
  - ***Acute multiple sclerosis***
  - **Fatal familial insomnia**
  - **Spinal cord lesion ***
  - **Acute intermittent porphyria ***
  - **Acute bulbar poliomyelitis ***
  - **Baroreflex failure ***
  - ***Cushing's disease or syndrome***
  - ***Renal/ renin-secreting tumor***
  - ***Acute coronary insufficiency* +/- myocardial infarct) ***
  - ***Hypersensitivity reactions ****
  - ***Hypothalamic tumor ****
  - ***Fibrosarcoma in pulmonary artery ****
  - **Pheochromocytoma ***
  - **Neuroblastoma */ Ganglioneuroma ***
  - **Gastroenteropancreatic neuroendocrine tumor ***
  - **Intracranial-pressure-causing lesions ***
  - **Guillian-Barre syndrome ***
  - **Hypoglycemia ***
  - **Clonidine withdrawal**
  - ***Mastocytosis***

Sample within-group lab tests showing spottiness of data

TABLE 1. Plasma Biochemical Tests (chronological order) in a patient with secondary hypertension, unknown cause

Date	Dopamine Frac Plasma (pg/mL)	Norepinephrine (pg/mL)	Epinephrin (pg/mL)	Normetanephrine Frac Free (nmol/L)	Metanephrine Frac Free (nmol/L)	DHPG Plasma (pg/mL)	DOPA Plasma (pg/mL)
10/21/03	30 (0-30)	444 (70-750)	283 (0-110)	0.28 (< 0.90)	0.21 (< 0.5)		
8/24/04	16 (0-30)	270 (70-750)	76 (0-110)	< 0.20 (< 0.89)	< 0.20 (< 0.49)		
(NIH)10/19/04	8 (3-46)	163 (80-498)	20 (4-83)			811 (518-1408)	1159 (911-2483)
11/23/04	15 (0-30)	448 (70-750)	68 (0-110)	<0.20 (< 0.89)	< 0.20 (< 0.49)		
1/14/05				0.39 (< 0.89)	<0.20 (<0.49)		
1/20/05	<10 (0-30)	326 (70-750)	19 (0-110)				
1/27/05	<10 (0-30)	411 (70-750)	37 (0-110)	0.44 (0.18-0.71)	0.12 (<0.49)		
2/28/05	<10 (0-30)	430 (70-750)	18 (0-110)				
3/15/05				0.20 (0.18-0.71)	0.08 (<0.49)		

Table 2. Urinary Biochemical Tests (Chronological Order, Abnormals = Shaded) in a Patient with Catecholamine-Secreting Enzymes from Unknown Cause

Date	Ur Metanephrines Total (mcg/24hr)	Ur Metanephrines (mcg/24hr)	Ur Norepinephrines (mcg/24hr)	Ur Epinephrines (mcg/24hr)	Ur Dopamine (mcg/24hr)	Ur VMA (mg/24 hr)	Ur Dopamine:Ur Creatinine Ratio (mcg/mcg)
3/28/93	0.42 (0.1-0.9)						
8/27/03	620 (0-1300)	500 (0-400)	55.8 (12.1-85.5)	12.4 (1.7-22.4)	341 (65-400)	2.5 (1.4-6.5)	
8/30/03							
10/7/03							
11/27/03							
12/10/03							
6/14/04							
8/17/04							
8/27/04	750 (95-475)	664 (19-140)	49.0 (15.0-100.0)	25.0 (2.0-24.0)	480 (52-480)	3.7 (1.4-6.5)	
9/29/04	600 (95-475)	414 (19-140)	42.0 (15.0-100.0)	12.0 (2.0-24.0)	476 (52-480)	5.4 (< 6.0)	0.4034 (< 0.28)
10/1/04			192* (15.0-100.0)	72.0* (2.0-24.0)	2424* (52-480)		
10/3/04	1362 (95-475)	1098 (19-140)	66 (15.0-100.0)	18.0 (2.0-24.0)	630 (52-480)	6.6 (<6.0)	0.3728 (< 0.28)
10/5/04			264* (15.0-100.0)	48.0* (2.0-24.0)	1384* (52-480)		
10/7/04	187.3* ((95-475)	10.1* (19-140)	127.6* (15.0-100.0)	38.5* (2.0-24.0)	872.3* (52-480)	9.5* (<6.0)	
12/21/04							
12/23/04							
12/27/04	383 (95-475)	241 (19-140)	53 (15.0-100.0)	14 (2.0-24.0)			
1/28/05		142* (19-140)	90* (15.0-100.0)	26* (2.0-24.0)	370* (52-480)	6.4* (<6.0)	
6/05							
7/05							

(Legend: Graytone = Abnormal. *=Extrapolated to 24-hour volume and concentration from spot collections < 24-hr Collections)

Features of HPT event-history data

- Selective patient measurement (both i and t)
- Sustained HPT vs. paroxysmal HPT
- DDX: Many biochemical lab tests possible, errors high
- DDX: Plasma +/- Urinary metanephrines and catecholamines testing?
- Same things not measured every time, unbalanced: epinephrine, norepinephrine, chromogranin A or its fragments, neuropeptide Y, Dopamine B-hydroxylase (DBH), HVA, VMA, dopamine, serotonin
- Diurnal variation normal ... Or flipped in reverse
- Postural hypotension, positional HPT possible
- Spikes during sleep (not) associated with changes in heart rate ... CONTINUED ...

Features of HPT event-history data (cont'd)

- Dietary interferences to tests
- Drug interferences to tests
- Ambulatory blood pressure monitoring (ABPM) "capturing" a paroxysm IFF known stimulus used
- Provocational testing highly sensitive and specific but risky in inexperienced hands, costly (time, $)
- Missing data if ABPM moves ... Or if acute paroxysm HPT exceeds machine's range
- Labs and/or ABPM missing in a clump ... Or missing only intermittently ... Or selectively drawn
- MD doesn't know when trigger to paroxysm began or ended w.r. to test window
- HPT paroxysm 1-5 minutes if APUD, ABPM interval is 15-20 minutes. Event coding is hit-or-miss.

Event-history model forms extendable to all model classes*

1. Fixed effects
    1. One-way -- But clinical skepticism about assumption
    2. Two-way – But no autocorrelation correction in SW?
2. Random effects
    1. Only constant term is random, no heterogeneity in the mean
    2. Product of densities for patient's group, not sum of logs, must be computed, individual density like .25 means if group size is ~100, end result is more rounding error than result.

Event-history model forms extendable to all model classes* (cont'd)

3. Random coefficients
   1. Coefficients on exogenous variables may be random or fixed
   2. Distribution of parameters may be modelled with other specific characteristics. Mean of distribution of β_j may vary deterministically across patients. Autocorrelation possible
4. Latent classes
   1. Most appealing clinical assumptions' compatibility
   2. Probability of observing y_{it} given that regime j applies ... Estimate class membership
   3. Latent heterogeneity model can be extended by allowing measured influences in the prior probability, due to time-invariant variables ... But time-invariance of variables is clinically problematic

Elegant toolkit, difficult clinical data

- All 4 model forms support all model classes used in cross-sections ... Binary choice, multinomial choice, count data, loglinear models, limited dependent variables models, survival models, switching models and stochastic frontier models

- All 4 model forms require for each group i (=patient) attached to each t^{th} record the variable ti = # repeated measures or the within-group # observations in the group ... Hard to handle

- Missing data confuse event-history set-ups
- Lab measure (t) has different reference range (t+s)

Software's treatment of missing data: evils of two lessers?

- Remove observations containing missing values from sample before estimation thus altering the ti or altering the group mix and/or also the patient mix since missing status is unlikely to be random!
- Leave observations in analysis (depending on SW, model class used). Estimator may bypass missing data.
- Observation count must give group sizes including missing values. Ought to be reported descriptively.
- Fixed effects estimator is shaky if Ti< 5 for some groups i.e. patients' time-series
- Random effects estimator may blow up if Ti is large for some groups (e.g. monitored often in treatment)

Canned event-history data-manipulation utilities needed

- Date handling and date-conversion to a whole hierarchy of time expressions
- "Spell" and "interval" matching, i.e. match lab tests on fixed dates with clinical, genetic, HPT, or other medical "event" data that are "around" the same time (clinicial/ analyst chooses from among semi-standardized "rules" for matching x_t, y_{t+s}
- Characterize with shape or time-series descriptive parameters each individual's grouped values. Examples: median, temporal "skew", distributional parameter just to describe shape of individual's group values

Canned event-history data- manipulation utilities needed (cont'd)

- Convert the data from calendar-time-level to event-time-level and to match data between formats
- Save, edit and reuse the above matching rules and conventions chosen so dataset can be grown cheaply as clinical data expands on a patient pool
- Multiple missing-data options for multiple variables, easy recount and recalc of the groups' ti's as choice of variable causes redefinition of #missing on the fly
- Coding multi-episode data by rule set used for matching (since matches' success often drive count of episodes per patient); exploratory graphics too
- Coding alphanumeric values uniquely in a hierarchy of levels. Example: Patient names => index variable

Statisticians' role uncovering "great mimic" apudomas: Event-history data utilities for *faster* clinical analyses

- "Curable in 90% (30-50% if malignant) of patients but eventually lethal in almost 100% if untreated"
- Time to diagnosis 2-7 years (metasizes by then if malignant)
- Cause of malpractice claims: "MD missed the diagnosis ... MD failed to diagnosis apudoma-caused HPT *rapidly* enough to avoid catastrophic disability or death ... MD treated patient with β blocker without preliminary α blockade ... Surgeon manipulated apudoma unknowingly and blew up patient's brain ... BP 255/125 in OR"

Acknowledgements

- William M. Manger, MD, PhD and Ray W. Gifford, MD. Pheochromocytoma: Clinical and Experimental, 2nd ed. Cambridge: 1996.
- Karel Pacak, MD, PhD, DSci, NIH/ NICHD, Chief, Endocrinology Unit and Graeme Eisenhofer, PhD, NIH/ NICHD